OMB Number: 4040-0001
Expiration Date: 06/30/2011

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. * TYPE OF SUBMISSION
☐ Pre-application ☒ Application ☐ Changed/Corrected Application

2. DATE SUBMITTED: 12/02/2010

Applicant Identifier:

4. a. Federal Identifier: AA020132

b. Agency Routing Identifier:

5. APPLICANT INFORMATION

*** Organizational DUNS:** 608195277

* Legal Name: The University of North Carolina at Chapel Hill
Department: Division:
* Street1: 104 Airport Drive, CB 1350
Street2: Suite 2200
* City: Chapel Hill County / Parish: Orange
* State: NC: North Carolina Province:
* Country: USA: UNITED STATES * ZIP / Postal Code: 27599-1350

Person to be contacted on matters involving this application
Prefix: * First Name: Brigid Middle Name: H
* Last Name: Poole Suffix:
* Phone Number: (919) 962-4673 Fax Number: (919) 962-2537
Email: bhpoole@email.unc.edu

6. * EMPLOYER IDENTIFICATION *(EIN) or (TIN):* 1-566001393-A1

7. * TYPE OF APPLICANT: H: Public/State Controlled Institution of Higher Education
Other (Specify):
Small Business Organization Type ☐ Women Owned ☐ Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION:
☐ New ☒ Resubmission
☐ Renewal ☐ Continuation ☐ Revision

If Revision, mark appropriate box(es).
☐ A. Increase Award ☐ B. Decrease Award ☐ C. Increase Duration ☐ D. Decrease Duration
☐ E. Other (specify):

* Is this application being submitted to other agencies? Yes ☐ No ☒ What other Agencies?

9. * NAME OF FEDERAL AGENCY: National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:
TITLE:

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:
Now versus Later decision Making: Effects of frontal development and alcohol use

12. PROPOSED PROJECT:
* Start Date: 07/01/2011 * Ending Date: 06/30/2014

*** 13. CONGRESSIONAL DISTRICT OF APPLICANT**: NC-004

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: * First Name: Christopher Middle Name: Thomas
* Last Name: Smith Suffix:
Position/Title: Graduate Student
* Organization Name: The University of North Carolina at Chapel Hill
Department: Psychology Division: College of Arts & Sciences
* Street1: Department of Psychology
Street2: Davie Hall, CB 3270
* City: Chapel Hill County / Parish: Orange
* State: NC: North Carolina Province:
* Country: USA: UNITED STATES * ZIP / Postal Code: 27599-3270
* Phone Number: 919-962-8340 Fax Number:
* Email: cts2014@email.unc.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	105,446.00
b. Total Non-Federal Funds	0.00
c. Total Federal & Non-Federal Funds	105,446.00
d. Estimated Program Income	0.00

16. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ☒ PROGRAM IS NOT COVERED BY E.O. 12372; OR

☐ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious. or fraudulent statements or claims may subject me to criminal, civil, or administrative penalities. (U.S. Code, Title 18, Section 1001)

☒ *** I agree**

**** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.***

18. SFLLL or other Explanatory Documentation

Add Attachment | Delete Attachment | View Attachment

19. Authorized Representative

Prefix: Dr. * First Name: Barbara Middle Name:

* Last Name: Entwisle Suffix: Ph.D.

* Position/Title: Interim Vice Chancellor for Research

* Organization: The University of North Carolina at Chapel Hill

Department: Office of Sponsored Research Division: Research

* Street1: 104 Airport Drive, Suite 2200

Street2: CB 1350

* City: Chapel Hill County / Parish: Orange

* State: NC: North Carolina Province:

* Country: USA: UNITED STATES * ZIP / Postal Code: 27599-1350

* Phone Number: (919) 966-3411 Fax Number: (919) 962-3352

* Email: resadminosr@unc.edu

*** Signature of Authorized Representative**: Barbara Entwisle

*** Date Signed**: 12/02/2010

20. Pre-application

Add Attachment | Delete Attachment | View Attachment

424 R&R and PHS-398 Specific
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 08/31/2011

Project/Performance Site Location(s)

Project/Performance Site Primary Location ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The University of North Carolina at Chapel Hill

DUNS Number: 6081952770000

* Street1: Departments of Psychology

Street2: Davie Hall, CB 3270

* City: Chapel Hill County: Orange

* State: NC: North Carolina

Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code: 27599-3270 * Project/ Performance Site Congressional District: NC-004

Project/Performance Site Location 1 ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:

DUNS Number:

* Street1:

Street2:

* City: County:

* State:

Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code: * Project/ Performance Site Congressional District:

Additional Location(s) Add Attachment Delete Attachment View Attachment

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? ☒ Yes ☐ No

1.a If YES to Human Subjects

Is the Project Exempt from Federal regulations? ☐ Yes ☒ No

If yes, check appropriate exemption number. ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

If no, is the IRB review Pending? ☒ Yes ☐ No

IRB Approval Date:

Human Subject Assurance Number:

2. * Are Vertebrate Animals Used? ☐ Yes ☒ No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ☐ Yes ☐ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. * Is proprietary/privileged information included in the application? ☐ Yes ☒ No

4.a. * Does this project have an actual or potential impact on the environment? ☐ Yes ☒ No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ☐ Yes ☐ No

4.d. If yes, please explain:

5. * Is the research performance site designated, or eligible to be designated, as a historic place? ☐ Yes ☒ No

5.a. If yes, please explain:

6. * Does this project involve activities outside of the United States or partnerships with international collaborators? ☐ Yes ☒ No

6.a. If yes, identify countries:

6.b. Optional Explanation:

7. * Project Summary/Abstract CSmith_ProjectSummary_11_28_101002900 Add Attachment Delete Attachment View Attachment

8. * Project Narrative CSmith_ProjectNarrative_11_28_1010029 Add Attachment Delete Attachment View Attachment

9. Bibliography & References Cited CSmithReferenceCited1002900496.pdf Add Attachment Delete Attachment View Attachment

10. Facilities & Other Resources Smith_Facilities1002900296.pdf Add Attachment Delete Attachment View Attachment

11. Equipment Smith_Equip1002900297.pdf Add Attachment Delete Attachment View Attachment

12. Other Attachments Add Attachments Delete Attachments View Attachments ☒

7. Project Summary/Abstract

Individuals are at greatest risk for developing an alcohol use disorder (AUD) during late adolescence (Kandel and Logan, 1984; Brown et al., 2008), possibly due to the relative impulsiveness of late adolescents/young adults. Kandel and Logan (1984) have suggested that the decline in heavy alcohol use that typically occurs in the mid-twenties may reflect a maturational or developmental process, as the development of frontal structures implicated in self-regulation and impulse control is complete in humans around the early-to-mid twenties (Giedd, 2004; Hooper et al., 2004; Rubia et al., 2006; Eshel et al., 2007). Although there is general acceptance of the idea that frontal circuits are still maturing in late adolescents no work to date has specifically investigated changes in the function of frontal circuits engaged during *Now* versus *Later* decision making, a quantifiable measure of impulsiveness. The proposed studies will compare late adolescents (ages 18-*23*) and adults (ages *25*-40) using *functional* MRI approaches to identify differences in the brain areas engaged during *Now* versus *Later* decision-making. In addition, we will determine whether heavy alcohol use is associated with abnormalities in normally observed age-related differences in these neural circuits. Our *central hypothesis* is that immaturity in frontal circuits and relatively increased signaling in striato-limbic structures promote impulsive decision making in late adolescents. We will test our central hypothesis via the following *Specific Aims*: **1) Indentify functional differences in frontostriatal circuits associated with *Now/Later* decision making in late adolescents versus adults.** *2) Determine whether the impulsive decision-making observed in heavy drinking adults is associated with signs of functional immaturity in frontal circuits.*

To achieve the goals of this research plan, a previously validated delay-discounting task (Mitchell et al., 2005; Boettiger et al., 2007) will be used to measure *Now/Later* decision making behavior in late adolescents and adults in the context of functional MRI. *We will seek to determine whether age-dependent differences in the function of brain structures of interest correlate with age-dependent differences in decision-making.* These studies will be conducted in both moderate and heavy drinking populations to determine how alcohol use impacts age-related changes in brain structures engaged in *Now/Later* decision making.

This research stands to significantly improve our understanding of the neural underpinnings of changes in decision-making from late adolescence to adulthood, which may bear on why late adolescents are at an increased risk for developing alcohol use disorders. Greater knowledge of the mechanisms underlying risk for developing alcohol use disorders may allow for the development of better treatments or interventions.

8. Project Narrative

This research project seeks to understand the neurobiological bases for the decline in the tendency to choose smaller, sooner rewards ("*Now*") over larger, later rewards ("*Later*") from late adolescence to early adulthood, a tendency that also characterizes individuals with alcohol use disorders. Studying developmental changes in the *function of* frontal structures that regulate *Now/Later* decision-making may provide insight into why late adolescents are at increased risk for developing alcohol use disorders, which may in turn aid in the development of new prevention and treatment approaches for this vulnerable age group.

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FACILITIES & OTHER RESOURCES

Environment – Contribution to Success:

The facilities and other resources available to the Sponsor's research team at UNC Chapel Hill include everything needed to successfully undertake and complete the proposed research project. When she set up her office and adjacent laboratory, they were equipped with this specific project in mind. These resources are complemented by the multitude of shared resources detailed below. Close proximity of all resources and consultants minimizes barriers to project execution and communication. The intellectual environment is rich with other extramurally-funded investigators conducting complementary research. For example, within the Psychology Department, Dr. Gina Carelli is conducting research investigating the role of dopamine in regulating response selection in rats. Dr. Carelli is the director of the Behavioral Neuroscience Program, to which the Sponsor belongs, and also serves on the Sponsor's faculty mentoring committee. The Behavioral Neuroscience Program has a long-standing NIDA training grant, which is available to initially support the Sponsor's trainees. The department's Cognitive Program includes several faculty members, including Dr. Joe Hopfinger, conducting neuroimaging research, with whom the Sponsor holds regular joint meetings; Dr. Hopfinger also serves on the Sponsor's mentoring committee. In addition to these departmental intellectual resources, the sponsor is also a member of the Bowles Center for Alcohol Studies, the Graduate Curriculum in Neurobiology, and the Biomedical Research Imaging Center. Through these associations, the PI will have access to numerous colleagues conducting relevant cognitive, neuroimaging, and addiction research as well as to two additional NIH training grants (in the Bowles Center and Neurobiology Curriculum) available for trainee support. Together these facilities provide a scientific environment that is strongly supportive of the proposed research and will therefore aid in its success.

Although the Sponsor is relatively junior, there is extensive evidence of UNC's commitment to her development as an academic researcher. Her 12-month, tenure-track academic appointment includes a total of three person months (25% effort) dedicated to research, with the option to buy out of one course per year allowing for an additional 3 person months (a total of 50% effort) dedicated to research. In addition, she was awarded an KL2 Translational Scholar Award through the UNC Clinical and Translational Science Award (See NC TraCS under "Other Resources"), which provides three years of salary support, allowing 75% effort dedicated to research; she is currently in year 2 of this award. Moreover, in 2009 Dr. Boettiger was selected as the UNC applicant for two highly competitive private grants: the Pew Scholars Program in the Biomedical Sciences, and the Dana Foundation Brain and Immuno-Imaging Grant Program. The start-up package provided to her included laboratory space, equipment and research funds needed to launch her research program. The package was sufficient to yield the preliminary data needed for this NRSA application. In addition, the sponsor, as a core faculty of the UNC Biomedical Research Imaging Center has been provided with unrestricted access to the MRI facilities and generous startup funds dedicated to scanner time, which will be available to fund the proposed studies. Administrative support is provided to the PI by a Behavioral Neuroscience Program Assistant, as well as a Psychology departmental administrative core that provides grants management, accounting, human resources, and instructional support. Important career-development programs are also available to the PI through NCTraCS and workshops offered through the UNC Center for Faculty Excellence on topics such as creating effective teaching portfolios, and grantsmanship. In addition, NC TraCS provides ongoing opportunities for research pilot funding, for which the PI is eligible to apply.

Facilities:

Laboratory: The Sponsor's lab is assigned 350 sq ft of laboratory space in the Psychology Department (Davie Hall). It is subdivided into a general computer workstation area, a behavioral subject testing area, and a wet lab area for biological sample storage and processing; this space is 100% dedicated to the Boettiger Lab's research. This space includes computer workstations to analyze fMRI data, computer-based testing facilities with high-quality graphics and timing routines for testing subjects, wet lab bench space, and all other resources (email, fax, on-line library catalogs) to facilitate research, writing and collaborations. Testing facilities include two separate testing rooms, both equipped with stimulus display, subject response devices, infrared camera monitors, and intercom communication. The wet lab is adjacent to the workstation and testing area and provides all necessary equipment for biological sample storage, handling, and processing, including refrigerator, freezer, flammables storage, vortexer/shaker, waterbath, full set of pipettors, Sorvall 6000G and Thermo Pico Fuge benchtop centrifuges, sink and eyewash. The lab is Biosafety Level-2 certified. An

additional 750 sq ft is available in the adjacent building (Howell Hall), which is also 100% dedicated to the Sponsor's research. This space includes a third private testing facility, which includes a mock MRI scanner equipped with full sound and visual display capabilities. This mock scanner facility is 100% dedicated to the Sponsor's research. The Howell Hall space also includes a private waiting area for subjects and separate office space (150 sq ft). The Boettiger Lab has access to dedicated parking spaces for research participants behind Davie Hall, and a common bus route stops outside of Davie Hall. *These laboratory facilities were specifically designed and equipped to support the program of research that includes the project proposed here.*

Biohazard Facilities The Boettiger is BSL-2 certified by the UNC Office of Environmental Health and Safety. Certification includes approval of a written lab safety plan, annual surprise audit, and annual training for all lab personnel. The facilities meet all necessary safety standards and include adequate materials and procedures for dealing with spills or other accidents. ***Note:*** *No research with select agents will be conducted.*

As a core faculty member of the Biomedical Research Imaging Center (BRIC), the sponsor and her research team have full access to its neuroimaging facility and its personnel. See *Equipment* section for greater detail on the BRIC facility. The BRIC is a 15 minute walk across campus from the Boettiger Lab, and also has dedicated parking in front of the building for research participants. The BRIC is also on a common bus route, and a campus bus runs frequently between the two locations. Public transit in Chapel Hill is free of charge, thus there are no significant access barriers to participation at either location.

Office: The Sponsor's office is adjacent to her laboratory. The personnel shared office space has hardwired high-speed internet access, as well as access to the internet via the UNC wireless network, and is equipped with four individual desks, four task chairs, two vertical filing cabinets, and 3 2-drawer filing cabinets, color and B/W laser printers (Davie Hall). Additional office space with four individual desks, four task chairs, two filing cabinets, and a color laser printer is available in the Howell Hall space. *These facilities will enable the PI to formulate experiments, analyze results, supervise undergraduate research assistants, and prepare manuscripts for publication.*

Computing: The Sponsor's lab is equipped with two high-end Linux machines, one of which includes a 1T RAID server. These computer workstations are 100% dedicated to processing and analysis of neuroimaging data. Additionally, the Sponsor's Lab is equipped with 4 Windows XP PCs dedicated to behavioral data collection, and analysis, and Windows XP/Vista desktops (8) and laptops (4), which personnel may use for behavioral paradigm development, off-site subject testing, data processing, and writing up study results. The Sponsor's Lab also has 500GB of dedicated space on a Windows fileserver in Davie Hall, which is backed up daily. Lab software includes Matlab, E-Prime, PASW, Microsoft Office, and Adobe Creative Suite. For additional storage and processing of neuroimaging data, the PI has access to large scale Linux fileservers located in the BRIC and accessible locally within the neuroimaging facility or over the network from the Sponsor's Lab. Workstations are also provided within the BRIC for neuroimaging data processing. The BRIC fileservers are backed up daily to a remote location in Cary, North Carolina.

Clinical: In the case of adverse events, the BRIC facility is equipped with a crash cart and is also located approximately 5 minutes from the UNC Hospital Emergency Room.

Animal: Not applicable.

Other Resources:

- Mammalian Genotyping Core Facility located on the UNC Campus. The sponsor has access by appointment on a fee-for-service basis. This facility routinely provides rapid and economical ABI TaqMan SNP (single nucleotide polymorphism) and small insertion/deletion genotyping. Such genotyping is suitable for a few to tens of SNPs to be typed for hundreds of samples. The core director, Dr. Jason Luo, will also collaborate with investigators, including providing services beyond genotyping that are important for ensuring the quality of genotyping project. Services include rigorous quality management, and several levels of quality control. In our previous experience with this core, they have provided high-quality results within 48 hours of sample submission.
- North Carolina Translational and Clinical Sciences (NC TraCS) Institute, funded in 2008 with an NIH Clinical and Translational Science Award, aims to support translatable research along every point of the research cycle from discovery to application, to dissemination, to practice and policy change, and back to rediscovery. Principal Investigator of the NC TraCS Institute is Dr. Etta Pisano, Vice Dean for

Academic Affairs in the UNC-CH School of Medicine, Kenan Professor of Radiology and Biomedical Engineering, and Director of the Biomedical Research Imaging Center (BRIC). Notably, as BRIC director, Dr. Pisano played a key role in recruiting the Sponsor to UNC. Through a pilot grant program, the NC TraCS Institute *has a total of $4.3 million available per year to support basic, clinical, and public health scientists* for discovery-to-bedside and bedside-to-practice translational research. As a member of the NC TraCS institute, the PI is eligible for the TraC$2K and TraC$10K Pilot Grant programs ($2,000 and $10,000, respectively, for one year), and the Large Pilot Program ($50-100K for one year). *Based on the translational nature of the proposed research, it is highly suitable for support from NC TraCS. As evidence of this, the Sponsor has already been a recipient of two of these grants ($2k and $50k).*

- NC TraCS Biostatistics Core is housed on the UNC campus and is directed by Michael Kosorok, PhD, Professor and Chair of the Biostatistics Department in the School of Public Health. The Biostatistics Core provides a variety of collaborative services to current NC TraCS Institute projects, and it extends the reach of the Institute by helping investigators across UNC-CH develop new projects. The Biostatistics Core consults with investigators about appropriate statistical techniques for different research designs, power and sample size calculations, data management strategies, and analysis of existing data. Statistical collaborations with KL2 scholars (including the Sponsor) are provided via the NC TraCS Institute's Education, Training, and Career Development Core with involvement from Biostatistics Core faculty, who have a broad range of expertise in analysis of clinical trials, observational studies, imaging, genetics, and outcomes research, and can provide general consultation about all phases of research design and analysis.
- NC TraCS Clinical and Translational Research Center (CTRC) (11,000 sq ft) is located on the third floor of UNC Memorial Hospital. The CTRC is available to assist in any clinical needs of the proposed project. For example, the PI has received training through the CTRC to collect blood via venipuncture or finger prick, which could be useful in the proposed studies. The CTRC has two outpatient facilities, which offer waiting rooms, outpatient examination rooms, interview rooms, a centralized nursing station, and a room used for the measurement of height, weight, and vital signs. A phlebotomy room is fully equipped for blood sample processing. Coverage is 24 hours a day, seven days a week for the Memorial Hospital location.

EQUIPMENT

In the Sponsor's Lab (Davie Hall): RAID fileserver. Wet lab includes a refrigerator, freezer, waterbath, flammables storage cabinet, Sorvall 6000G and Therm PicoFuge benchtop centrifuges, sink, and eyewash, for storage, processing and handling of saliva samples for DNA extraction. Mock MRI scanner equipped with full sound and visual display capabilities. Wet lab (bench and storage) are Biosafety Level 2, which allows for blood collection and blood sample storage.

In the Psychology Department (Davie Hall): Boettiger Lab personnel have complete access to a μQuant microplate spectrophotometer, which is used to quantify DNA sample concentrations.

In the BRIC: This Center within the UNC-Chapel Hill School of Medicine has a Siemens Allegra 3.0T head-only MRI scanner and a Siemens Tim Treo 3.0T whole-body MRI scanner, both of which are 100% dedicated to research. Staff of the Center includes a full time physicist, Dr. Weili Lin (Director of the Neuroimaging facility, *see Letter of Support*), three full time Research Associates responsible for fMRI data acquisition and facilities management, and a computing systems administrator. Personnel in Dr. Lin's lab also provide complementary support for MR sequence development and hardware modification. The Center provides limited pilot scanning free of charge, and additional funds for scanning may be available in extenuating circumstances. The BRIC also provides free access to a mock MRI scanner on site, and private rooms and restroom facilities for participant screening, post-scan testing, and pre-scan waiting periods.

Section II--Sponsor and Co-Sponsor Information

a. Research Support Available

Sponsor's Current Support

Funding Source	I.D. number	Title	P.I.	Dates	Amount
UNC, Chapel Hill	N/A	Start-up Funds	Boettiger	07/07-06/12	$367,000
NIH/NCRR	1KL2RR025746	UNC Clinical Translational Science Award-K12 Scholars Program (KL2)	Pisano	07/08-04/11	$85,000
UNC-CH Junior Faculty Development Award	N/A	Neuropharmacology of Immediate Reward Bias	Boettiger	01/10-12/10	$7,500
NC TraCS Institute NC TraC$50K Pilot	50KR20902	Neurocognitive Predictors of Naltrexone Response	Boettiger	10/09-6/11	$50,000

Pending Support

Funding Source	I.D. number	Title	P.I.	Dates	Amount
NIH/NIDA	R01 DA030381	Neuropharmacology of Immediate Reward Bias in Human Subjects	Boettiger	6/11-5/16	$1,250,000

b. Sponsor's/Co-Sponsor's Previous Fellows/ Trainees

Graduate students: 1 total (**1 current**)

Christopher T. Smith (BS, Furman University) PhD Student, Neurobiology Curriculum. 2009-present

Post-doctoral fellows: 2 total (**2 current**)

Mary K. Kelm (PhD, Pharmacology, UNC-Chapel Hill) 2009-present. *F32 fellowship from NIAAA pending.*

Vicki W. Chanon (PhD, Cognitive Psychology, UNC-Chapel Hill) 2007-present. Dr. Chanon *is supported by an F32 fellowship (DA025442)*; Dr. Boettiger is the sole sponsor on this award.

Co-Sponsor's Current Fellows/ Trainees (Fulton T. Crews)

*Graduate students: 7 total (**0 current**)*

Leon Coleman (MD/PhD, Neurobiology Curriculum, UNC-CH) 2007-2010
Current Position: Medical Student, UNC-CH

*Post-doctoral fellows: 13 total (**1 current**)*

Mary Katherine (Katie) Kelm (PhD, Pharmacology, UNC-CH) 2010-present.

Kim Nixon (PhD, UT-Austin) 2000-2005.
Current Position: Asst. Professor, University of Kentucky

Judson Chandler (PhD, UT-Austin) 1990-1994.
Current position: Assoc. Professor, MUSC

Rueben Gonzales (PhD, UT-Austin) 1983-1986.
Current Position: Professor, UT-Austin

c. Training Plan, Environment, Research Facilities

Training plan: Chris Smith has been working in my laboratory since May 2009. In that time, he has made significant progress towards his goal of developing expertise in cognitive neuroscience techniques for the purposes of investigating the neurobiology of alcohol use disorders. To help him achieve his career goal, his training will primarily focus on the following areas: research development, oral and written communication skills, and ethical training. Towards the end of the fellowship period his training will also include guidance in the areas of mentoring/teaching. Although Chris' proposed research is not clinical in nature, it does bear on a clinical issue, thus he will also receive some training as to the clinical aspects of addiction.

Research Development: As Chris arrived in the lab with no human research, he requires training in all aspects of initiating studies, conducting cognitive experiments, executing fMRI studies, and analyzing data.

Study Initiation. Chris has contributed to the design of the experiments outlined in this application from their

inception. He contributed to the development of the Institutional Review Board (IRB) protocol for the preliminary studies included in the Research Plan, and *has developed* the protocol for the proposed experiments. This process was educational for him in terms of understanding how to properly implement informed consent. He will submit the IRB protocol for the proposed studies shortly after submitting this fellowship application. While IRB protocol development can be somewhat onerous, it is a skill that he will need in order to successfully conduct independent human subjects research.

Cognitive Behavioral Experiments. Since arriving in the lab, Chris has become expert in the administration of the delay discounting task to be used in the proposed studies. He used the task both during his rotation project in the Spring of 2009, and while collecting preliminary data for this proposal (see *Research Plan – Aims 1 and 2 Justification and Feasibility*). Notably, each of these projects has resulted in a first-authored Abstract for Chris. He presented his rotation project data at the 2010 Cognitive Neuroscience Society meeting, and presented his preliminary studies data at the 2010 Research Society on Alcoholism meeting. *He is currently preparing manuscripts for publication based on this work.* In the course of these projects, he became familiar with the program we use to design computerized tasks and to collect behavioral data (E-Prime) and the program we use to analyze the data (MATLAB). These experiences using E-Prime and MATLAB will be useful in the future when Chris may wish to create different cognitive tasks and analyze behavioral data. Although Chris' undergraduate coursework included substantial training in cognitive psychology, he will take (or audit) one or two graduate courses here at UNC that will augment his training in this area. Three particularly relevant courses are a Behavioral Decision Theory course (PSYC 433), a general Cognitive Neuroscience course (PSYC 434), and a Translational Seminar in Cognitive and Clinical Neuroscience (NBIO 727).

Functional MRI Experiments. Dr. Boettiger will provide Chris with direct training in all aspects of fMRI research. In addition, I will provide funds for Chris to attend an fMRI short course offered at the New Mexico MIND Institute, as I have for my other lab personnel. Chris will also have access to local UNC workshops on use of the software package Statistical Parametric Mapping (SPM8). In addition to me, within my lab Chris will have an additional mentor in his labmate Dr. Vicki Chanon, who has completed two fMRI studies to date. As evidenced by Dr. Weili Lin's letter of support, Chris will have access to ample expertise within the BRIC that will complement my own. In addition to the support and training offered through the BRIC, the UNC Developmental Neuroimaging Core also provides training in the analysis of fMRI, sMRI, and DTI data. The director of this core, Dr. Aysenil Belger, is a fellow member of the Neurobiology Curriculum and a colleague with whom I regularly interact. *Finally, in October Chris began collecting fMRI data for a collaborative study in which he is using the same delay discounting task and acquisition parameters as those for his proposed studies. He has also begun the initial steps of fMRI analysis with these data. Thus, working on this project has helped to prepare Chris to conduct the fMRI studies proposed here.*

Data analysis. To analyze the behavioral studies, we will use Predictive Analytics SoftWare (PASW-formerly SPSS). Chris has experience with PASW through analysis of his preliminary studies. He will also take a short course offered by the UNC Odum Institute in his first year of training that will cover all of the capabilities of PASW. My lab uses SPM8 for MRI data analysis, and Chris attended an SPM8 basics course at UNC last Spring led by researchers from the Martinos Center for Biomedical Imaging at Harvard University. Course content included preprocessing, statistical modeling, and visualizing neuroimaging data. Chris will spend a considerable amount of time on learning how to analyze fMRI data. He will receive guidance primarily from me, and the Biomedical Research Imaging Center (BRIC) image analysis core on the analysis and interpretation of his data.

Oral and Written Communication Skills: To improve Chris' oral communication skills, in addition to the didactic training provided in the Neurobiology Curriculum, he will also present monthly at our weekly lab meeting. Although this is an informal setting generally including only our research group, I expect presentations in a format suitable for a larger audience. I will encourage Chris to attend Psychology, Bowles Center for Alcohol Studies, and Neuroscience seminars for exposure to different presentation styles and to gain up-to-date information. Chris will present his data at national and international conferences, such as Research Society on Alcoholism, Society for Neuroscience, Cognitive Neuroscience Society, College on Problems of Drug Dependence, and the Organization for Human Brain Mapping. He will attend two of these meetings per year. In addition to improving his oral communication skills by presenting his data, attending these meetings will enable him to establish scientific relationships beyond UNC.

To improve his written communication skills, Chris will prepare manuscripts for publication and abstracts for

the meetings he will attend. He has *published* two abstracts based on his work thus far, which I expect to continue during the period of this fellowship. Data collection and analyses for the two behavioral studies that form the basis of his submitted abstracts *is nearly complete, and he has begun to* prepare manuscripts for *submission*, as reflected in the *Research Plan – Timeline.* In addition to the writing skills he has gained through the preparation of this application, he will contribute to future grant preparation in my laboratory. By presenting at lab meetings and conferences, attending seminars, and preparing manuscripts, grants and abstracts, I expect Chris to develop the oral and written communication skills necessary for scientific success.

Ethical Training: Chris has completed the Collaborative Institutional Training Initiative (CITI) training, which includes information on the history and ethical principles of human research, IRB regulations and review processes, informed consent, data records maintenance and management, vulnerable subjects, conflicts of interest, privacy, confidentiality, and HIPAA. To ensure that the MRI studies are conducted as safely as possible, he has completed an online course on bioeffects, safety and patient management for magnetic resonance procedures; this is required annually for all BRIC members. Through the UNC Environment, Health and Safety Department, he has completed lab environment and bloodborne pathogens courses.

As part of the Neurobiology Curriculum, Chris has received didactic training in the ethical conduct of scientific research. This training was designed to meet NIH standards and has been extensively reviewed in association with UNC's Neurobiology T32 training grant. Topic areas include: conflict of interest, data management, publication and peer review, intellectual property, use of animal and human subjects, university guidelines of research, and handling misconduct. He will expand upon this ethics training during the first year of this award when he will take a responsible conduct of research course through NCTraCS (see *Facilities – Other Resources)* to serve as a refresher for the CITI training. Most importantly, an environment has been established in my lab in which trainees are encouraged to engage in continued discussions regarding ethical issues with me as a part of their research training experience. This aspect of training is particularly important as it is recognized that lectures alone cannot cover all potential ethical concerns that can arise in the course of scientific research. This combination of experiences will ensure that Chris is well-versed in ethical issues.

Mentoring/Teaching: Chris will gain mentoring experience during this fellowship by supervising undergraduate research assistants in the lab. This will give him experience in managing individuals in a mentored environment, which will aid him when he moves on to a more independent stage of his career. Because Chris ultimately hopes to attain a faculty appointment that includes a teaching component, he will pursue opportunities to teach during his fellowship. These could involve being a guest lecturer or teaching assistant in Behavioral Neuroscience (Psychology) or Physiology (Biology) courses. In addition, he will participate in workshops offered by the UNC Office of Faculty Excellence on syllabus development, overcoming teaching anxiety, and creating effective assignments and presentations.

Clinical Training: Chris and I both feel that it is important for him to appreciate the clinical side of alcoholism. For this reason, Chris attends a weekly meeting with Dr. J.C. Garbutt and Dr. Alexei Kampov, who conduct clinical research in the area of alcohol use disorders (AUDs). In these meetings we discuss collaborations ongoing between our groups, including studies of behavioral risk-factors for AUDs in late adolescents, which is particularly pertinent to Chris' proposed studies. These meetings have been invaluable in exposing Chris to the clinical concerns related to his own studies. Chris also attends the Bowles Center for Alcohol Studies lecture series, which includes basic science and clinical talks. Chris will also participate in a Bowles Center outing to the UNC Alcohol and Substance Abuse Program (ASAP) and Triangle Residential Options for Substance Abusers (TROSA). At the ASAP facility, he will learn about common characteristics of substance abusers. TROSA is a highly structured program that provides two years of free residential treatment for substance abusers in a community-oriented environment. During the TROSA tour, Chris will interact with residents to learn about the TROSA program and their struggle with addiction. Because Chris envisions future research projects focused on alcoholism, participation in all these activities will keep him up to date on current research and help him in developing his postdoctoral plans.

In summary, Chris Smith's training will consist of coursework, seminars, colloquia, formal meetings with faculty advisors, *including members of his thesis committee,* as well the research plan he has outlined in the present proposal. In addition to the training he will receive in my laboratory, there is an abundance of opportunities for didactic training in addiction science and functional neuroimaging at UNC Chapel Hill, which will complement Chris' existing expertise in basic neurobiology and cognitive psychology. *In addition, courses on human cognitive development and human neuroanatomy, offered at neighboring Duke University, will provide didactic*

training pertinent to Chris' proposed studies. Chris will take advantage of graduate course offerings within UNC's Behavioral Neuroscience program, including the Research Seminar Series in Experimental Psychology (co-Directed by *dissertation committee member,* Dr. Regina Carelli), which is supported by the program's NIDA training grant for "Research on Drug Abuse", and is thus focused on that topic. As Director of the addiction-focused Behavioral Neuroscience program, of which I am a member, Dr. Carelli will provide Chris with additional mentorship in this area. Dr Carelli's commitment to Chris' success is evident in her willingness to support Chris' first *two* years in my lab through the Behavioral Neuroscience Program's T32 training grant. Dr. Linda Dykstra, the training grant Co-Director is also committed to Chris' success, as additionally evidenced by her reference letter, and she will also provide critical senior mentorship to Chris. In addition, UNC Chapel Hill hosts a large number of visiting speakers who are expert in the biology and psychology of drug and alcohol addiction through three independent colloquium series sponsored by the Psychology Department, the Graduate Curriculum in Neurobiology, and the Bowles Center for Alcohol Studies. Moreover, there is ample opportunity to gain exposure to clinical aspects of addiction through the treatment wing of the Bowles Center, and the presentation and discussion of clinical findings through the Center's seminar series. Chris will attend the weekly group meetings of Dr. J.C. Garbutt, Director of Clinical Studies in the Bowles Center. In addition, the Center's Director, *Co-Sponsor,* Dr. Fulton Crews, will provide additional mentorship and guidance to Chris in the course of this fellowship; Dr Crews is also a member of Chris' Dissertation Committee. Thus, UNC Chapel Hill has a wide range of didactic and interactive seminars for gaining knowledge on issues pertinent to this proposal. In addition to attending these seminars, Chris will be able to interact on a one-to-one basis with a range of faculty based here at Chapel Hill in Psychology, Neurobiology, Psychiatry, Radiology, and the Bowles Center. Given my relative inexperience as a mentor, these senior colleagues will provide valuable additional guidance to Chris, particularly in the areas of grantsmanship and other aspects of professional development. With regard to grantsmanship, I will encourage Chris to use some of the funds that would accompany this NRSA to attend an NIH regional course on grantwriting. Closer to home, this year he attended a one-day UNC course on this topic directed toward early career investigators. The forums and senior colleagues mentioned above will also be instrumental in providing guidance and feedback when Chris is ready to apply for postdoc positions.

Within my lab, weekly meetings of all personnel are held to discuss current projects and recent journal articles relevant to our research. We also have a joint lab meeting on a recurring basis with other UNC faculty engaged in neuroimaging research, including Aysenil Belger, Kelly Giovanello, and Joseph Hopfinger, to discuss matters specific to fMRI.

In his first year of this fellowship, I expect that Chris will take a course each semester in order to cultivate expertise in cognitive neuroscience and multivariate statistics, which will complement his strong background in neurobiology. He will also attend selected talks and seminars when they are relevant, meet with addiction clinicians at the Bowles Center, and initiate his research plans. In his second year, I expect that he will continue to attend relevant talks, and complete his initial data collection and analysis and write up the preliminary results of his research. I expect his third year to be devoted primarily to the completion of his studies and preparation of results for publication. Each year, I also expect that he will present abstracts at the Society for Neuroscience annual meeting, as well as the annual meeting of either the Cognitive Neuroscience Society, the Organization for Human Brain Mapping, the Research Society on Alcoholism, or the College on Problems of Drug Dependence.

Table 1. Specific Skill Development Activities and Instructors

Skill	Activity	Mentor/Instructor
1. MRI methods; fMRI experimental design and data analysis	1. Training and supervision in fMRI experimental design, including issues of statistical power, signal strength, artifact reduction, novel data acquisition, and analysis techniques 2. Training and supervision in data analysis using software packages including SPM. 3. Training and supervision in data interpretation	Charlotte Boettiger, Ph.D. Weili Lin, Ph.D. Asyenil Belger, M.D., Ph.D. Hongtu Zhu, Ph.D. Gabriel Dichter, Ph.D.
	Attendance of the BRIC seminar series	BRIC Members

2. Specific issues regarding alcohol use disorders	Directed readings, training and supervision regarding substance abuse issues in research	Charlotte Boettiger, Ph.D J.C. Garbutt, M.D.
3. Advanced biostatistics	Consultation with BRIC faculty (Biostatistics)	Hongtu Zhu, Ph.D.
4. Advanced training in theoretical issues of the neurobiological bases of addiction	1. Attendance at the Behavioral Neuroscience Seminar at UNC-CH focused on the neural mechanisms of addictive behavior 2. Attendance of the Bowles Center for Alcohol Studies seminar series	Charlotte Boettiger, Ph.D. Regina Carelli, Ph.D. Fulton T. Crews, Ph.D. Linda Dykstra, Ph.D. J.C. Garbutt, M.D.
5. Publication and presentation of research results; writing grants, and training in the responsible conduct of research	Meetings with mentors to discuss progress of project, responsible conduct, appropriate avenues for presentation of preliminary results, publication of final results, and grantsmanship.	Charlotte Boettiger, Ph.D. Regina Carelli, Ph.D. Fulton T. Crews, Ph.D. Linda Dykstra, Ph.D. J.C. Garbutt, M.D.

Environment and research facilities: The combined resources of my own lab, the Psychology Department, the Biomedical Research Imaging Center, and the Bowles Center for Alcohol Studies, and the NC TraCS Institute will be available to Chris to support his research plans. These include:

Boettiger lab: Functional MRI laboratory with computer workstations to analyze data, computer-based testing facilities with high-quality graphics and timing routines for testing subjects, wet lab bench space, and all other resources (email, fax, on-line library catalogs) to facilitate research, writing and collaborations; ample office and lab space. Testing facilities include three separate testing rooms, one equipped with state-of-the art eye-tracking equipment (Tobii 1750), and one equipped with a mock scanner, and a third equipped with physiological monitoring equipment (BioPac Systems Inc.). My wet lab is adjacent to the workstation and testing area and provides all necessary equipment for biological sample storage, handling, and processing, including refrigerator, freezer, flammables storage, vortexer/shaker, waterbath, pipettors, Sorvall 6000G and Thermo Pico Fuge benchtop centrifuges, sink and eyewash. We have excellent access to a pool of research subjects from throughout the Chapel Hill campus and Research Triangle area. During the period of Chris' fellowship, I have dedicated funding for scanner time (included in start-up funds), of which I will commit a sufficient amount for Chris' studies. Any shortfall in the first year could be absorbed by my KL2 research funds of $25,000 - $35,000 per year. Additionally, pilot funds from the NC TraCS Institute or the Bowles Center for Alcohol Studies are other likely sources of funds for these studies. In addition, I have applied for R01 funding, which would fully and directly fund Chris' studies.

In the Department of Psychology: The department provides several key resources which support my lab's research mission. Such resources include shared equipment located within Davie Hall and thus easily accessible from our lab. We also have access to the Department's large participant pool, who may participate in our studies for credit, at no cost to the researcher. The department also provides full administrative support for IRB protocol and extramural grant submissions. In addition, we have access to the expertise of numerous senior faculty within the Behavioral Neuroscience program engaged in addiction neuroscience research.

In the Biomedical Research Imaging Center: This Center within the UNC-Chapel Hill School of Medicine has a Siemens Allegra 3.0T MRI scanner and a Siemens Tim Treo 3.0T whole-body MRI scanner that are both 100% dedicated to research. Staff of the Center includes a full time physicist, Dr. Weili Lin (Director of the Neuroimaging facility, *and likely new Director of the BRIC*), three full time Research Associates responsible for fMRI data acquisition and facilities management, an Imaging Analysis Core (Dr. Dinggang Shen, Director) and a computing systems administrator. The BRIC seminar series provides access to a wide range of neuroimaging expertise and a forum for critique of one's work. Dr. Hongtu Zhu, a BRIC faculty member expert in Biostatistics will be a particularly valuable influence in guiding Chris' approaches towards his data. As a BRIC faculty member, my lab is entitled to ample free data storage space on the BRIC servers as well as full access to the entire range of analytical software, including consultation. Moreover, these resources are accessible over a secure network from my laboratory in Davie Hall. Personnel in Dr. Lin's lab also provide complementary support for MR sequence development and hardware modification. The Center provides pilot scanning free of charge for up to three subjects per study, and additional funds for scanning may be available in extenuating circumstances. *In addition, in 2011, my lab will acquire space that is adjacent to that occupied by the labs of Drs. Lin and Shen. This will enable closer interaction between my lab members, including Chris, and these labs, which have a wealth of expertise in neuroimaging analysis, particularly sMRI, DTI, and multimodal analyses.*

In the Bowles Center for Alcohol Studies: The numerous faculty and postdocs within the Bowles Center possess relevant expertise spanning from basic addiction research to clinical treatment of substance abuse. As a faculty member of the Bowles Center, I have routine access to the personnel and resources of the Center.

In the UNC School of Medicine: In addition, to my primary appointment in Psychology, I have a 25% appointment in the BRIC, a part of the school of Medicine. I am also a member of the NC TraCS Institute and the Bowles Center for Alcohol Studies. Through the School of Medicine, several key resources are available to my lab, including the Developmental Neuroimaging Core (Dr. Aysenil Belger, Director).

Relationship of training to applicant's career: The proposed training will equip Chris with the knowledge and skills necessary to address a range of issues in addiction neuroscience, not limited to a single technique and not necessarily limited to the topic of the present proposal. A young scientist with Chris' background in basic neurobiology and psychology, who will gain training in addiction, cognitive neuroscience and neuroimaging will be ideally positioned to make major scientific contributions. The proposed fellowship training is the perfect avenue for Chris to learn to apply cognitive neuroscientific approaches towards studying behaviors linked to alcohol abuse. This new training will lead to his being highly qualified to pursue postdoctoral training at a major research university.

d. Number of Fellows/Trainees to be Supervised During the Fellowship

I anticipate that there will be 1-3 other trainees in my lab during the period of Chris' fellowship**,** which would result in a maximum of 4 trainees at any one time in the lab. Currently, in addition to Chris, I supervise two postdoctoral fellows. The NRSA application of the more senior fellow, Dr. Chanon, *was funded by* NIDA *in August 2010. The second post-doc, Dr, Kelm, recently received an excellent score on her NRSA application.* I intend to maintain a mixture of post-docs and graduate students in the lab, as I feel that the students benefit from secondary mentors within the lab, and post-docs benefit from the opportunity to practice mentoring more junior scientists.

e. Applicant's Qualifications and Potential for a Research Career

Chris was enthusiastically recruited by the highly selective BBSP program at UNC, which suggests that he is one of the promising young academic biomedical scientists of his age cohort. My own interactions with him have been entirely consistent with this evaluation. I was impressed with Chris when I interviewed him for the BBSP program and was delighted when he approached me about rotating in my lab during his first year. Despite lacking any practical experience with the type of work we do in my lab, Chris was one of the most productive members of the lab during his brief (2 month) rotation. He not only learns new skills extremely quickly and readily and easily imparts those skills to others, he is extraordinarily diligent and meticulous in his approach to data analysis. Chris *is already showing this same aptitude for neuroimaging methods, and* I am completely confident that he will master all of the necessary skills for this proposal in rapid fashion. I can say without reservation that I am very pleased with the decision to accept Chris into my lab as a graduate student.

Chris is a very bright and internally motivated scientist. He is a clear thinker, and he has shown great creativity and initiative in designing his research program. He voraciously pursues the literature in an effort to contextualize his ideas and his results. In addition, he has demonstrated himself to be a consistent, dedicated, and detail-oriented experimentalist. Moreover, he demonstrates equal enthusiasm for data analysis. This aptitude for research enabled him to collect sufficient data to submit first-authored abstracts, based on two different studies, to the Cognitive Neuroscience Society and Research Society on Alcoholism (RSA) meetings. I also note that Chris received a student merit travel award to attend the RSA meeting based on his submission. Chris demonstrates a growing aptitude for presenting his ideas in different forums and I am confident that his commitment to this aspect of his career will help to make him an excellent teacher as well as researcher.

In summary, Chris has outstanding intellectual potential and is pursuing a line of inquiry that is highly relevant to NIAAA's mission. He demonstrates a level of maturity and ability that exceeds my expectations for more senior graduate students. Moreover, Chris is fully committed to following a career in research on alcoholism. In this proposal, he will clearly be able to build expertise in new areas by drawing upon my experience in cognitive neuroscience, addiction, and fMRI. Thus, he will be uniquely qualified to address future questions related to the neurobiological bases of alcohol use disorders using numerous research tools. For these reasons, I feel that Chris will develop into a leading alcohol researcher. I am highly supportive of Chris' NRSA proposal and I am delighted to be working with him as his sponsor on this project.

UNC SCHOOL OF MEDICINE
BOWLES CENTER FOR ALCOHOL STUDIES

November 18, 2010

Re: Christopher Smith

To the review committee:

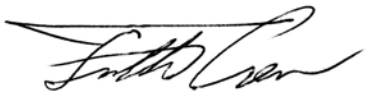
I am pleased to be a co-sponsor for Christopher Smith for this pre-doctoral NRSA Award. As Director of the Bowles Center for Alcohol Studies with decades of neuroscience research investigation, I have gained a broad knowledge of alcohol action. One particular area on which my work has focused is the effect of ethanol on the adolescent brain. Thus, my expertise is highly relevant to Chris' proposed research. I have known Chris since he was a first year graduate student, when he spent time in the lab of my colleague in our Center for Alcohol Studies, Dr. Clyde Hodge. I currently serve on Chris' dissertation committee, and I look forward to continuing to contribute to his training. Initially, we plan to meet monthly to review his activities and progress. I have started neuroimaging experiments in my own laboratory, so I will be able to provide him with technical guidance as well during out meetings. I will also help to guide his future career with advice on manuscript preparation, scientific presentations, and securing a postdoctoral position. Chris is dedicated and bright and I believe that he will develop and achieve his ultimate goal of running his own laboratory.

The quality and quantity of work that Chris has managed to produce during the short time he has been in his thesis lab are noteworthy. He received a 2010 Student Travel Award from RSA, and I expect that more awards will follow as he continues to make contributions to the field. As a member of Chris' thesis committee, I have observed firsthand how Chris endeavors to form clear hypotheses and design thoughtful experiments, and thoroughly analyze his data. I believe he is as capable as my other students who have gone on to become successful academic alcohol researchers, e.g. Rueben Gonzales, Judson Chandler and Kim Nixon.

I have had the pleasure of working closely with Chris' mentor, Dr. Boettiger. We wrote a review together on impulsivity and alcohol, mixing human and animal studies. Charlotte Boettiger is an emerging star in alcohol studies, having discovered the frontal cortical actions of naltrexone. I think Dr. Boettiger will be an excellent mentor on the cutting edge of neuropsychology and imaging research. I will provide more global guidance and mentoring.

In summary, Chris Smith is an outstanding candidate for support by an individual NRSA pre-doctoral fellowship. He is intelligent, creative, highly-motivated and well-trained. He brings a valuable background to his proposed studies. He has demonstrated his ability to work productively, and has a strong commitment to the study of alcohol addiction. I am excited to be playing a role in Chris' future success by serving as a co-sponsor on this application.

Sincerely,



Fulton T. Crews, Ph.D.
Director of the Bowles Center for Alcohol Studies
John Andrews Distinguished Professor
Professor of Pharmacology and Psychiatry
CB# 7178, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

Phone (919)966-5678 • Fax (919)966-5679

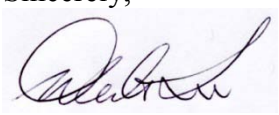
UNC
SCHOOL OF MEDICINE
DEPARTMENT OF
RADIOLOGY

November 19, 2010

To whom it may concern:

I am happy to support the NRSA application of Christopher Smith as a Doctoral Fellow in the lab of Dr. Charlotte Boettiger. The Boettiger lab has full access to the imaging facilities of the Biomedical Research Imaging Center (BRIC) at UNC-Chapel Hill. The BRIC currently has a Siemens Allegra 3.0T head-only MRI scanner and a Siemens Tim Trio 3.0T whole-body MRI scanner that are 100% dedicated to research. In addition to the scanners in our imaging core, Chris will have access to our image analysis core and biostatistics core, which includes extensive expertise in the structural MRI and DTI techniques that will complement the fMRI expertise of Dr. Boettiger.

Sincerely,



Weili Lin, PhD
Professor and Vice Chair of Basic Research, Radiology
Professor of Biomedical Engineering and Neurology
Associate Director, Biomedical Research Imaging Center

List of Referees:

Linda A. Dykstra, Ph.D., Department of Psychology, University of North Carolina at Chapel Hill

Judith E. Grisel, Ph.D., Department of Psychology, Furman University

Clyde W. Hodge, Ph.D., Departments of Psychiatry and Pharmacology, University of North Carolina at Chapel Hill

Donita Robinson, Ph.D., Department of Psychiatry, University of North Carolina at Chapel Hill

Gabriel S. Dichter, Ph.D., Departments of Psychiatry and Psychology, University of North Carolina at Chapel Hill; Department of Psychiatry and Behavioral Sciences, Duke University Medical Center

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | * First Name: Christopher | Middle Name: Thomas
* Last Name: Smith | Suffix:
Position/Title: Graduate Student | Department: Psychology
Organization Name: The University of North Carolina at Chapel Hill | Division: College of Arts & Sciences
* Street1: Department of Psychology
Street2: Davie Hall, CB 3270
* City: Chapel Hill | County/ Parish: Orange
* State: NC: North Carolina | Province:
* Country: USA: UNITED STATES | * Zip / Postal Code: 27599-3270
* Phone Number: 919-962-8340 | Fax Number:
* E-Mail: cts2014@email.unc.edu

Credential, e.g., agency login: CTS2014

*** Project Role:** PD/PI | **Other Project Role Category:**

Degree Type: BS
Degree Year: 2008

***Attach Biographical Sketch** Smith_NRSA_applicant_fellowbi | Add Attachment | Delete Attachment | View Attachment
Attach Current & Pending Support | Add Attachment | Delete Attachment | View Attachment

PROFILE - Senior/Key Person 1

Prefix: | * First Name: Charlotte | Middle Name: A
* Last Name: Boettiger | Suffix:
Position/Title: Asst Prof | Department: Psychology
Organization Name: The University of North Carolina at Chapel Hill | Division:
* Street1: CB:304 B Davie Hall
Street2:
* City: Chapel Hill | County/ Parish: Orange
* State: NC: North Carolina | Province:
* Country: USA: UNITED STATES | * Zip / Postal Code: 27599-3270
* Phone Number: (919) 962-2119 | Fax Number: (919) 962-2537
* E-Mail: cab@unc.edu

Credential, e.g., agency login: cboettiger

*** Project Role:** Other (Specify) | **Other Project Role Category:** Sponsor

Degree Type: PhD
Degree Year: 2000

***Attach Biographical Sketch** Boettiger_biosketch1002900301 | Add Attachment | Delete Attachment | View Attachment
Attach Current & Pending Support | Add Attachment | Delete Attachment | View Attachment

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 2

Prefix: | * First Name: Fulton | Middle Name: T

* Last Name: Crews | Suffix:

Position/Title: Dir, Dir Center For Alcohol Studies, Prof | Department: Pharmacology

Organization Name: The University of North Carolina at Chapel Hill | Division:

* Street1: CB:7178 1021 Thurston-Bowles

Street2:

* City: Chapel Hill | County/ Parish: Orange

* State: NC: North Carolina | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 27599-7178

* Phone Number: (919) 966-5678 | Fax Number: (919) 966-5679

* E-Mail: fulton_crews@med.unc.edu

Credential, e.g., agency login: ftcrews

*** Project Role:** Other (Specify) | **Other Project Role Category:** Co-Sponsor

Degree Type: PhD

Degree Year: 1978

***Attach Biographical Sketch** Crews_biosketch1002900498.pdf | Add Attachment | Delete Attachment | View Attachment

Attach Current & Pending Support | Add Attachment | Delete Attachment | View Attachment

FELLOWSHIP APPLICANT BIOGRAPHICAL SKETCH

USE ONLY FOR INDIVIDUAL PREDOCTORAL and POSTDOCTORAL FELLOWSHIPS. DO NOT EXCEED FOUR PAGES.

NAME OF FELLOWSHIP APPLICANT	POSITION TITLE
Christopher Thomas Smith	Graduate Student, Curriculum in Neurobiology
eRA COMMONS USER NAME (credential, e.g., agency login) CTS2014	

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Furman University	B.S.	05/2008	Neuroscience
University of North Carolina, Chapel Hill	Ph.D.	12/2014	Neurobiology

Please refer to the application instructions in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement

My long term research interests involve understanding the neurobiology of alcohol use disorders and particularly the cognitive processes related to problem alcohol use. My academic training and research experience have provided me with a strong background in behavioral neuroscience. Courses in cell and molecular neurobiology and the biological bases of behavior have provided me with a broad understanding of neurobiology from the molecular to behavioral level. While at my undergraduate institution, I worked in a basic behavioral neuroscience lab focused on understanding the relationship of beta-endorphin to depression and anxiety in a mouse model, and how alcohol may act through beta-endorphin to alter behavior. *This work prompted me to pursue graduate study in the neurobiology of alcohol addiction at the University of North Carolina at Chapel Hill. After discovering the value of human research in approaching the complex problem of addiction through a first-year rotation as part of UNC's Biological and Biomedical Science Program,* I joined my thesis lab in June 2009, and since that time, I have been investigating the neurobiology of decision making processes in human subjects with a special emphasis on decisions between immediate and delayed rewards ("*Now*" versus "*Later*"). My work in the lab thus far has resulted in several (4) published abstracts for national meetings, including two first-author abstracts. The proposed research will allow me to gain experience in neuroimaging techniques and provide me with the ability to use the tools of magnetic resonance imaging (MRI) to better understand the neurobiology of *Now/Later* decision making from a developmental prospective and how alcohol use may impact this decision making at functional and neuroanatomical level. In addition, the proposed training plan will allow me to improve the analytical and scientific communication skills I will need to be a successful independent investigator in the future. My choice of Dr. Charlotte Boettiger as my advisor and the strengths of her lab and the Bowles Center for Alcohol Studies at UNC will provide me with the necessary skills to reach my goal of studying the neurobiology of alcohol use disorders in humans *using behavioral, cognitive, and neuroimaging experimental approaches*.

B. Positions and Honors

ACTIVITY/OCCUPATION	BEGINNING DATE (mm/yy)	ENDING DATE (mm/yy)	FIELD	INSTITUTION/COMPANY	SUPERVISOR/ EMPLOYER
America Counts, America Reads Tutor	11/06	05/08	Academic tutoring	Stone Academy of Communication Arts	Connie Buto
Summer Research Fellow	06/07	09/07	Behavioral Neuroscience	Furman University	Dr. Judith E. Grisel

Academic and Professional Honors

South Carolina Governor's School at the College of Charleston Summer Experience Participant, 2003
South Carolina Palmetto Fellow, 2004-2008
Furman Scholar, 2004-2008
South Carolina NIH-IDeA Networks of Biomedical Research Excellence Summer Research Fellowship, 2007
B.S. awarded with high honors, Furman University, 2008
Research Society on Alcoholism Student Merit Travel Award, 2010
Graduate Mentor Award from UNC Office of Undergraduate Research, Summer 2010

Memberships in professional societies:

Society for Neuroscience (2007-present)
Cognitive Neuroscience Society (2009-present)
Research Society on Alcoholism (2009-present)

C. Publications

Abstracts:

Smith CT, Cloonan G, Lee A, Grisel JE (2007). Role of β-endorphin in behavioral despair, stress, and anxiety. Society for Neuroscience 2007 Annual Meeting.

Smith CT, Boettiger CA (2010). Ovarian Cycle Effects on Immediate Reward Bias: a Window on PFC Dopamine. Cognitive Neuroscience Society 2010 Annual Meeting.

Smith CT, Freeman-Daniels E, Boettiger CA (2010). Effects of Gender, Age, and Alcohol Use Behavior on Impulsive Decision Making. Research Society on Alcoholism 2010 Annual Meeting.

Chanon VW, **Smith CT**, Kalka LS, Kampov-Polevo AB, Garbutt JC, Boettiger CA (2010). Effects Of Naltrexone On Alcohol Attentional Bias And Delay Discounting: A Pilot Study. Research Society on Alcoholism 2010 Annual Meeting.

Boettiger CA, **Smith CT** (2010). Immediate Reward Bias in Humans: Effects of Alcohol Use, Dopamine, Hormones, Age, and Gender. Clinical and Translational Research and Education Meeting. Washington D.C.

Acknowledgements:

Grisel JE, Bartels JL, Allen SA, Turgeon VL (2008). Influence of *β*-endorphin on anxious behavior in mice: interaction with EtOH. *Psychopharmacology*, *200*, 105-115.

D. Scholastic Performance

YEAR	SCIENCE COURSE TITLE	GRADE	YEAR	OTHER COURSE TITLE	GRADE
	FURMAN UNIVERSITY			FURMAN UNIVERSITY	
2004	Fundamentals of Chemistry I	A	2005	Vectors and Matrices (Math course)	A
2005	Fundamentals of Chemistry II – Inorganic Chemistry	A	2005	General Psychology	A
2005	Foundations of Biology	A+	2006	Statistics (Economics course)	B
2005	Fundamentals of Chemistry III – Organic Chemistry	A-	2006	Social Psychology	B
2006	Genetics	A-	2007	Psychometrics and Assessment (Psychology course	A-
2006	Spectroscopy and Molecular Structure (Chemistry course)	A+	2007	Learning (Psychology course)	A-

YEAR	SCIENCE COURSE TITLE	GRADE	YEAR	OTHER COURSE TITLE	GRADE
2006	Experimental and Statistical Methods (Psychology course)	A-	2008	Memory and Cognition (Psychology course)	A
2007	Human Physiology	A-	2008	Brain and Mind (Interdisciplinary studies course)	A-
2007	Introduction to Biopsychology	A-			
2007	Biological Chemistry	C+			
2007	Current Topics in Neuroscience	A			
2008	Behavioral Neuroscience	B			
2008	Neurobiology	A			
	UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL				
2008	Introduction to Genetic Analysis	P			
2008	Introduction to Cell and Molecular Neurobiology (CMNB)	H			
2008	CMNB - Cell Signaling	P			
2008	CMNB - Electrical Signals	H			
2008-9	BBSP 1st Year Seminar in Research Ethics and Scientific Communication	P			
2009	CMNB - Synaptic Mechanisms	H			
2009	CMNB - Anatomy and Function	P			
2009	Biological Bases of Behavior II	H			
2009	Developmental Neurobiology	P			
2009	Behavioral Pharmacology	P			
2009-10	Scientific Communication Seminar	H			

UNC Chapel Hill graduate courses are graded H (high pass), P (pass), L (low pass) or F (fail). *Passing is B or better.*

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Boettiger, Charlotte A	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) cboettiger	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of California, Berkeley	A.B.	05/93	Integrative Biology
University of California, San Francisco	Ph.D.	12/00	Neuroscience
University of California, San Francisco	Postdoctoral	06/01	Psychiatry
University of California, Berkeley	Postdoctoral	08/03	Psychology

A. Personal Statement

The goal of the proposed research is to identify functional brain changes from *early (18-23) to later (25-40) adulthood* that correlate with age-dependent changes in immediate reward bias in humans. Clarifying the neurobiology of immediate reward bias, particularly how it may differ between life stages with differential risk for substance use disorders, will significantly advance our ability to identify new targets and strategies for preventing and treating such disorders. My expertise is well suited to successfully mentor the proposed work. I have a broad background in neuroscience, with specific training and expertise in key research areas for this application. As a postdoctoral fellow at UC Berkeley, I carried out functional neuroimaging (fMRI) investigating the neurobiological underpinnings of a form of executive function. At the Ernest Gallo Clinic and Research Center at the UC San Francisco, I expanded my research to include behavioral pharmacology and neuroimaging studies of decision-making behavior in control and alcoholic populations. As PI on a DOD-funded project, I laid the groundwork for the proposed research by developing an IQ-independent delay discounting task with high test-retest reliability, which is fMRI compatible. In addition, I successfully administered the projects (e.g. staffing, research protections, budget, and progress reports), which were conducted off-site at Berkeley, and produced (to date) four peer-reviewed publications from the project*, with a fifth under review.* As a result of these previous experiences, I am aware of the importance of meticulous logistical planning, which is required for successful neuroimaging studies with humans. The current application builds logically on my prior work, and our environment provides additional expertise in structural neuroimaging techniques. In summary, I have demonstrated my capacity for successful and productive research in an area of high relevance to addictive disorders, and my expertise and experience will enable me to mentor the proposed project.

B. Positions and Honors

Positions and Employment

1992-1994	Research Asst., University of California, Berkeley, Molecular and Cell Biology Dept.
2001	Postdoctoral Fellow, University of California, San Francisco, Psychiatry Dept.
2001-2003	Postdoctoral Fellow, University of California, Berkeley, H. Wills Neuroscience Institute
2003-2005	Assistant Research Scientist, Ernest Gallo Clinic & Research Center (EGCRC)
2005-2007	Associate Investigator, EGCRC
2005-2007	Adjunct Assistant Professor, Neurology Dept., University of California, San Francisco
2007-	Assistant Professor, Psychology Dept. & Biomedical Research Imaging Center, University of North Carolina, Chapel Hill (UNC-CH)
2007-	Graduate Faculty Member, Curriculum in Neurobiology, UNC-CH
2008-	Faculty Member, Bowles Center for Alcohol Studies, UNC-CH

Other Experience and Professional Memberships

1994-	Member, American Association for the Advancement of Science
1996-	Member, Society for Neuroscience
2001-	Member, Cognitive Neuroscience Society
2005-2007	Founding President & Representative, San Francisco Bay Area Chapter of the Society for Neuroscience
2007	Medical Research Council (London), ad hoc reviewer
2008	NIAAA Special Emphasis Panel: Behavioral Mechanisms in the Transition to Habitual Alcohol Seeking and Drinking, ad hoc reviewer
2009	NIAAA Scientific Review Group: Neuroscience Research Review Subcommittee (AA-4), ad hoc reviewer
2009-	Member, Research Society on Alcoholism
2010	*Behavioral and Social Advisory Council, Alcoholic Beverage Medical Research Foundation, ad hoc grant reviewer*
2010	*The Netherlands National Initiative Brain and Cognition, ad hoc grant reviewer*

Selected Honors and Awards

1992	University of California President's Undergraduate Fellowship
1993	HHMI U.C. Berkeley Undergraduate Biology Fellowship
1995	National Science Foundation Graduate Fellowship Honorable Mention
1995	UCSF Graduate Opportunity Fellowship
1997	Pre-doctoral National Research Service Award (NIH/NIMH)
1998	UCSF Graduate Dean's/Anthony Fellowship in Neuroscience
2001	McDonnell Summer Institute in Cognitive Neuroscience Fellowship
2002	Wheeler Center for the Neurobiology of Addiction Hugh O'Connor Memorial Fellowship
2009	IBM Junior Faculty Development Award, UNC-CH

C. Selected Peer-reviewed Publications

Most relevant

Boettiger CA, D'Esposito M. (2005) Frontal Networks for Learning and Executing Arbitrary Stimulus-Response Associations. Journal of Neuroscience, 25:2723-2732.

Mitchell JM, Fields HL, D'Esposito M, **Boettiger CA**. (2005) Impulsive Responding in Alcoholics. Alcoholism: Clinical and Experimental Research, 29:2158-2169.

Mitchell JM, Tavares VC, Fields HL, D'Esposito M, **Boettiger CA**. (2007) Regulation of Impulsivity by Endogenous Opioids in Alcoholics and Healthy Controls. Neuropsychopharmacology, 32:439-449

Boettiger CA, Mitchell JM, Tavares VC, D'Esposito M, Fields HL. (2007) Immediate reward bias in humans: fronto-parietal networks and a role for the catechol-*O*-methyltransferase 158(Val/Val) genotype. Journal of Neuroscience 27:14383-14391.

Boettiger CA, Kelley, EA, Mitchell JM, D'Esposito M, Fields HL. (2009) *Now or Later*? An fMRI study of the effects of endogenous opioid blockade on a decision-making network. Pharmacology Biochemistry and Behavior 93:291-299. PMCID: PMC2729462.

Crews FT, **Boettiger CA.** (2009) Impulsivity, Frontal Lobes and Risk for Addiction. Pharmacology Biochemistry and Behavior 93:237-247. PMCID: PMC2730661

Additional recent publications of importance to the field (in chronological order)

Boettiger CA, Doupe AJ. (1998) Intrinsic and thalamic excitatory inputs onto songbird LMAN neurons differ in their pharmacological and temporal properties. Journal of Neurophysiology, 79:2615–2628.

Boettiger CA, Doupe AJ. (2001) Developmentally restricted synaptic plasticity in a songbird nucleus required for song learning. Neuron, 31:809-818.

Doupe AJ, Solis MM, **Boettiger CA**, Hessler NA. (2004) Birdsong: Hearing in the Service of Vocal Learning and Production. In: The Cognitive Neurosciences III, 3rd Edition. M Gazzaniga, ed. pp 245-258. MIT press.

Boettiger CA, D'Esposito M (2006) Addiction. In: The Praeger Handbook of Learning and the Brain. S. Feinstein ed. pp 5-9 Greenwoood.

Boettiger CA. (2008) Endogenous Opioids and Impulsive Responding in Alcoholics and Healthy Controls. European Neuropsychopharmacology 18:S194.

Solis MM, Hessler NA, **Boettiger CA**, Doupe AJ (2008) Song selectivity, singing and synaptic plasticity in songbirds. In: Topics in Integrative Neuroscience: From Cells to Cognition. JR Pomerantz, ed. Pp 363-384. Cambridge University Press.

Chanon VM, **Boettiger CA** (2009) Addiction and Cognitive Control. A. Browne-Miller, ed. In: Praeger International Collections on Addictions. Vol. 2: Psychobiological Profiles. Praeger-Greenwood.

Garland E, Gaylord, SA, **Boettiger CA**, Howard MO (2010) Mindfulness training modifies cognitive, affective, and physiological mechanisms implicated in alcohol dependence: Results of a randomized controlled pilot trial. J Psychoactive Drugs 42:177-192.

*Chanon VW, Sours CR, **Boettiger CA** (2010) Attentional bias toward cigarette cues in active smokers. Psychopharmacology, 212:309-320.*

D. Research Support

Ongoing Research Support

F32 DA025442 *Chanon (PI)* *08/01/10 – 07/31/13*

Neurobiological Correlates of Attentional Bias in Addiction

Goal: to identify the neurobiological basis of attentional bias towards smoking cues in active smokers.

Role: Sponsor (Mentor)

UL1 RR025747 *Runge* (PI) 04/01/210 –03/31/11

UNC-CH Clinical Translational Science Award - NC TraC$2K Pilot Grant: Genotyping of neural correlates of attentional bias toward cigarette cues in active smokers

The goal of this study is to determine specific genetic polymorphisms correlate with brain activity associated with attentional bias towards cigarette cues in smokers.

Role: Pilot Project Mentor (Chanon, PI)

IBM Junior Faculty Development Award, UNC-CH Boettiger (PI) 01/01/10 – 12/31/10

Neuropharmacology of Immediate Reward Bias

The goal of this project is to collect pilot data on the effects of amino acid depletion on immediate reward bias in healthy adults.

UL1 RR025747 *Runge* (PI) 10/01/09 – *6/30/11*

UNC-CH Clinical Translational Science Award - NC TraC$50K Pilot Grant: Neurocognitive Predictors of Naltrexone Response

The goal of this study is to determine how well changes in two neurocognitive measures, immediate reward bias and alcohol attentional bias, predict treatment outcomes in a clinical trial of naltrexone for alcoholism.

Role: Pilot Project PI

UL1 RR025747 *Runge* (PI) 10/01/09 – 9/30/10

UNC-CH Clinical Translational Science Award - NC TraC$2K Pilot Grant: Frontal Dopamine and Immediate Reward Selection Bias

The goal of this study is to determine the effect of ovarian cycle on immediate reward bias in humans and how any such effect interacts with genotype at the Val158Met COMT polymorphism.

Role: Pilot Project PI

KL2 RR025746 *Runge* (PI) 05/19/08 – 04/30/11

Mentored Translational Scientist Award: to develop a neurocognitive research program with a focus on neurobiological markers of addictive disorders and laboratory predictors of therapeutic response in these diseases.

Role: Funded Scholar

Completed Research Support

DOD W81XWH-06-1-0240 White (PI) 01/01/04 – 12/31/08

Neural Circuit Responses to Alcohol and Naltrexone

The goal of this project was to identify brain activity associated with immediate reward bias in humans and to determine the effects of naltrexone on decision-making behavior and underlying brain activity.
Role: PI on peer-reviewed pilot project

F31 MH011896 Boettiger (PI) 10/01/97 – 09/30/00
Developmental Changes in the Circuit of a Songbird Nucleus
The goal of this project was to identify cellular and synaptic changes associated with sensory learning within the song-learning circuitry of the zebra finch.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Crews, Fulton T.	John R. Andrews Professor, Psychiatry and Pharmacology Director, Center for Alcohol Studies
eRA COMMONS USER NAME (credential, e.g., agency login) ftcrews	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Syracuse Univ., Syracuse, NY	B.S	1971	Physiology
Univ. of Michigan, Ann Arbor, MI	Ph.D.	1978	Pharmacology
National Institutes of Health, Bethesda, MD	Post Doc	1980	Pharmacology

A. Personal Statement:

I am happy to co-sponsor Chris Smith for this predoctoral NRSA Award. I have known him for several years and have followed his development. I look forward to the opportunity to meet with him and contribute to his training. I am a neuroscientist who has made considerable contributions to understanding the neurobiology of alcoholism and mechanisms of neurodegeneration. Recent discoveries have included ethanol inhibition of adult neurogenesis, ethanol and inflammation induction of innate immune genes in brain persist and increase oxidative stress for long periods leading to neurodegeneration. In addition, we have discovered that adolescents are much more sensitive to ethanol inhibition of neurogenesis and forebrain neurodegeneration than adults. Thus, the goals of Chris' proposed research are highly relevant to my own research program. Moreover, I have started neuroimaging experiments in my own laboratory, so I will be able to provide him with technical guidance during our meetings. I will also guide his future career with advice on funding, mentoring students, University bureaucracy and other issues to help him become a successful academic scientist. I think Dr. Boettiger will be an excellent mentor on the cutting edge of neuropsychology and imaging research. I will provide more global guidance and mentoring. Through this fellowship, I believe that Chris will develop the skills he will need to become an independent scientists, and ultimately achieve his goal of running his own lab.

B. Positions and Honors

Positions and Employment

1973-1978	NIH Training Awardee, Pharm, Univ of Michigan Rackham Grad School. (Advisor:Dr. C.B. Smith)
1978-1980	Pharmacology Research Associate Program Awardee, (Preceptor: Julius Axelrod). Staff Fellow, National Institute of Mental Health, Section on Pharmacology, Lab of Clinical Science.
1980-1994	Prof of Pharm, College of Medicine, University of Florida. (Assist, 1980- 1985, Assoc 1985-1990).
1994-Present	Director, Bowles Center for Alcohol Studies, Professor of Pharm and Psychiatry, SOM, UNC-CH.

Honors

1968	NY State Regents Scholar
1973	NIH Predoctoral Fellowship
1978	NIH PRAT Fellow
1987	Grass Scientist Award
1989-1991	NIMH Study Section, Psychopathology and Clinical Biology (PCB-2)
1990, 1992	Research Scholar Award University of Florida
1991-94	Member, National V.A. Merit-Grant Review Board: Alcoholism and Drug Dependence

1991-1994	Board of Directors, Division of Sponsored Research, Univ. of Florida
1991-1995	NIH Study Section: Alcohol Biomedical Research Review Committee (ALCB-2)
1992	NIH Javitts Grant Awardee
1993-Present	NIH Merit Grant Awardee
1993-1994	Chairman, National V.A. Merit-Grant Review Board: Alcoholism and Drug Dependence
1994-Present	Board of Directors, N.C. Governor's Institute on Substance Abuse
1995-1999	Research Society on Alcoholism Board of Directors
1995-Present	Board of Directors, Freedom House Treatment and Recovery Center
1996-Present	Board of Directors, Alcohol and Drug Council of North Carolina
1997-Present	Board of Directors, Pavillon Treatment Center
1998-2000	President, Alcohol and Drug Council of North Carolina
1999	Editorial Advisory Board, Betty Ford Center quarterly newsletter *Findings*
2001	Received the University of Michigan Outstanding Alumnus Award
2002	National Institute of Health Grand Rounds Speaker, Bldg. 10
2003	Forbes Lectureship, Grass Foundation Award, Chicago Chapter of Neuroscience
2003	Norbert Kelly Distinguished Award for Contribution to Understanding Addiction as a Mental Disease, Addiction Professionals of North Carolina, NCADC, Pinehurst N.C.
2004-Present	Chair, External Advisory Board for Research Portfolio Review, NIAAA
2009	WENDY AND STANLEY MARSH 3 Endowed Lectureship Univ of Texas 6/16-17/09
2009	Plenary Lecture Austrian Neuroscience Association, Salzburg AUSTRIA ,9/18/09
2009	Okey Memorial Lecture: Psychiatry Research Trust, London England 11/17/09

B. Selected Peer-reviewed Publications (Selected from over 200 publications).

Most relevant to the current application

1. Knapp, D.J., Braun C.J., Qian Y., Fernandes A., Duncan G.E., **Crews F.T.**, and Breese G.R. Regional specificity of ethanol and NMDA action in brain revealed with FOS-like immunohistochemistry and differential routes of drug administration. Alcohol:Clin Exp Res 25(11):1662-1672, 2001. PMID: 11707641
2. Obernier, J.A., White, A.M., Swartzwelder, H.S., and **Crews, F.T.** Cognitive deficits and CNS damage after a 4-day binge ethanol exposure in rats. Pharmacol Biochem Behav 72:521-532, 2002. PMID: 12175448
3. Kampov-Polevoy, A.B., Ziedonis, D., Steinberg, M.L., Pinsky, I., Krejci, J., Eick, C., Boland, G, Khalitov, E., **Crews, F.T.** Association between sweet preference and paternal history of alcoholism in psychiatric and substance abuse patients. Alchol Clin Exp Res, 27(12): 1929-1936, 2003. PMID: 14691380
4. Nixon, K., **Crews, F.T.** Temporally Specific Burst in Cell Proliferation Increases Hippocampal Neurogenesis in Protracted Abstinence from Alcohol. The Journal of Neuroscience, 24(43): 9714-9722, 2004. PMID: 15509760
5. **Crews, F.T.**, Boettiger, C.A. Impulsivity, frontal lobes and risk for addiction. Pharmacol Biochem Behav. 93 (3) 237-247, 2009 PMID: 19410598

Additional recent publications of importance to the field (in chronological order)

6. **Crews, F.T**. and SMITH, C.B.: Presynaptic *alpha*-receptor subsensitivity after long-term antidepressant treatment. Science 202:322-324, 1978. **PMID: 211589**
7. HIRATA, F., AXELROD, J., and **CREWS, F.T**.: Concanavalin A stimulates phospholipid methylation and phosphatidylserine decarboxylation in rat mast cells. Proc. Natl. Acad. Sci. *USA.* 76:4813-4816, 1979. **PMID: 92021**
8. **Crews, FT**., Summary Report of a Symposium: Genes and Gene Delivery for Diseases of Alcoholism. Alcohol Clin Exp Res 25(12):1778-1800, 2001. PMID: 11781512
9. Obernier, J.A., Bouldin, T.W., and **Crews, F.T.** Binge ethanol exposure in adult rats causes necrotic cell death. Alcohol Clin Exp Res 26(4): 547-557, 2002. PMID: 11981132
10. Nixon, K., **Crews, F.T.** Binge ethanol exposure decreases neurogenesis in adult rat hippocampus. Journal of Neurochem 83: 1087-1093, 2002. PMID: 12437579Crews, F.T., Miller, M.W., Ma, W., Nixon, K., Zawada, W.M., and Zakhari, S. Neural Stem Cells and Alcohol. Alcohol Clin Exp Res, 27(2): 324-335, 2003. PMID: 12605082
11. Bison, S. and **Crews, F.T.** Alcohol Withdrawal Increases Neuropeptide Y in Rat Brain. Alchol Clin Exp Res, 27(7): 1173-1183, 2003. PMID: 12878925

12. **Crews, F.T**. and Braun, C.J. Binge ethanol treatment causes greater brain damage in alcohol-preferring P rats than in alcohol nonpreferring NP rats. Alchol Clin Exp Res, 27(7): 1075-1082, 2003. PMID: 12878913
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14. **Crews, F.T.,** Nixon, K., Wilkie, M.B. Exercise Reverses Ethanol Inhibition of Adult Neurogenesis. Alcohol, 33(1): 63-71, 2004. PMID: 15353174
15. Kampov-Polevoy A.B., Eick C., Boland G., Khalitov E., **Crews F.T.** Sweet liking, novelty seeking, and gender predict alcoholic status. Alcohol Clin Exp Res, 28(9): 1291-1298, 2004. PMID: 15365298
16. Duka, T., Gentry, J., Malcolm, R., Ripley, T., Borlikova, G., Stephens, D., Veatch, L., Becker, H., **Crews, F.T.** Consequences of multiple withdrawal from alcohol. Alcohol Clin Exp Res, 28(2): 233-246, 2004. PMID: 15112931
17. **Crews, F.T.**, Colllins, M., Dlugos, C., Littleton, J., Neafsey, E.J., Pentney, R., Snell, L., Tabakoff, B., Zou, J., Noronha, A., and Wilkins, L. Alcohol-Induced Neurodegeneration: When, Where and Why? Alcohol Clin Exp Res, 28(2): 350-364, 2004. PMID: 15112943
18. He, J, Nixon, K., Shetty, A., and **Crews, F.T.** Chronic alcohol exposure reduces hippocampal neurogenesis and dendritic growth of newborn neurons. European Journal of Neuroscience, 21(10): 2711-2720, 2005. PMID: 15926919
19. **Crews, F.T.,** Mdzinarishvili, A., He, J., Kim, D., Nixon, K. Neurogenesis in adolescent brain is potently inhibited by ethanol. Neuroscience 137: 437-445, 2006. PMID: 16289890
20. Monti, P.M., Miranda, R. JR., Nixon, K., Sher, K.J., Swartzwelder, H.S., Tapert, S.F., White, A., and **Crews, F.T.** Adolescence: booze, brains, and behavior. Alcohol Clin Exp Res, 29(2): 207-20, 2005. PMID: 15714044
21. **Crews, F.T.**, Buckley, T., Dodd, P.R., Ende, G., Foley, N., Harper, C., and He, J. Alcoholic neurobiology: changes in dependence and recovery. Alcohol Clin Exp Res, 29(8): 1504-13, 2005. PMID: 16156047
22. Pandey, SC, Chartoff, EH, Carlezon, WA Jr, Zou, J, Zhang, H, Kreibich, AS, Blendy, JA, and **Crews, FT.** CREB gene transcription factors: role in molecular mechanisms of alcohol and drug addiction. Alcohol Clin Exp Res, 29(2): 176-84, 2005. PMID: 15714041
23. Zou, J.Y. and **Crews, F.T.** Tumor necrosis factor-potentiates glutamate neurotoxicity by inhibiting glutamate uptake in organotypic brain slice cultures. Brain Res, 1034: 11-24, 2005. PMID: 15713255
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25. **Crews, F.T.**, Bechara, R., Brown, L., Guidot, D., Mandrekar, P., Oak, S., Qin, L., Szabo G., Wheeler, M., Zou,J. Cytokines and Alcohol. Alcohol Clin Exp Res, 30(4): 720-730, 2006. PMID: 16573591
26. **Crews, F.T.**, Nixon, K., Kim, D., Joseph, J., Shukitt-Hale, B., Qin, L., Zou, J. BHT blocks NF-κB activation and Ethanol-Induced Brain Damage. Alcohol Clin Exp Res, 30(11): 1938-1949, 2006. PMID: 17067360
27. He, J., **Crews, F.T.** Neurogenesis decreases during brain maturation from adolescence to adulthood. Pharmacology, Biochemistry and Behavior, 86(2): 327-333, 2007. PMID: 17169417
28. **Crews, F.T.**, He, J., Hodge, C. Adolescent cortical development: a critical period of vulnerability for addiction. Pharmacology, Biochemistry and Behavior, 86(2): 189-199, 2007. PMID: 17222895
29. Qin, L., Wu, X., Block, M., Liu, Y. X., Breese, G., Hong, J.S., Knapp, D., **Crews, F.T.** Systemic LPS Causes Chronic Neuroinflammation and Progressive Neurodegeneration, GLIA 55: 453-462, 2007. PMID: 17203472
30. He, J., **Crews, F.T.** Increased MCP-1 and microglia in various regions of the human alcoholic brain. Exp Neurol, 210: 349-58, 2008. PMID: 18190912
31. Nicholas, P.C., Kim, D., **Crews, F.T.**, Macdonald,J.M. H NMR-based metabolomic analysis of liver, serum, and brain following ethanol administration in rats. Chem Res Toxicol. Feb;21(2):408-20, 2008. PMID: 18095657
32. Qin, L., He, J., Hanes, R. N., Pluzarev, O., Hong, J. S., **Crews, F. T.** Increased systemic and brain cytokine production and neuroinflammation by endotoxin following ethanol treatment. J Neuroinflammation 18:5-10, 2008. PMID: 18348728
33. Coleman, L.G. Jr, Jarskog, L.F., Moy, S.S., **Crews, F.T.** Deficits in adult prefrontal Cortex neurons and behavior following early post-natal NMDA antagonist treatment. Pharmacol Biochem Behav. 93 (3) 322-330. 2009 PMID: 19409920

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35. **Crews, F.T.**, Nixon, K. Mechanisms of neurodegeneration and regeneration Alcohol. Alcoholism. 44(2):115-27, 2009. PMID: 18940959
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37. Stevenson, J.R., Schroeder, J.P., Nixon, K., Besheer, J., **Crews, F.T.**, Hodge, C.W. Abstinence following alcohol drinking produces depression-like behavior and reduced hippocampal neurogenesis in mice. Neuropsychopharmacology. 34(5):1209-22, 2009.PMID: 18563059

D. Research Support

Ethanol Effects on Neurotransmission (Crews)
NIH/NIAAA
R01 (AA006069, Years 19-23) 3/1/04 - 7/31/10 No cost extension
This grant focuses on changes in cell genesis in rat brain using a 4 day binge model of alcohol dependence. Studies investigate changes in formation of neurons throughout brain during the development of physical dependence to alcohol and during withdrawal. These studies complement, but do not overlap with the current proposal. Role: Dr. Crews is PI and is involved in the design, analysis and publication of data.

*Molecular and Cellular Alcohol Research Training (Crews)
NIH/NIAAA
T32 (AA07573, Years 06-10) 4/1/03 - 3/31/13
The training grant promotes the development of promising PhD postdoctoral fellows as independent investigators and future faculty members who will investigate the pathogenesis of alcoholism and alcohol abuse using modern molecular medicine techniques.
Role: Dr. Crews is the key administrator.

*Molecular & Cellular Pathogenesis in Alcoholism (Crews)
NIH/NIAAA
5P60-AA011605 12/1/02-11/30/12
This P60 is focused on the unifying hypothesis that common cellular and molecular events caused by ethanol lead to alterations in cellular signaling that trigger tissue specific pathologies.
Role: PI

Completed Research Support (past 3 years)
Cerebral Metabolism of Ethanol-Derived Acetate (Nicholas) Crews Sponsor NIH/NIAAA
NRSA 8/01/06 – 7/31/09 Dr. Crews was mentor to Mr. Nicholas

*Molecular Mechanisms of Ethanol Reinforcement (Hodge)
NIH/NIAAA
R01 (AA014983, Years 5-10) 8/05/05 - 6/30/2010
The primary goal of this application is to characterize the involvement of metabotropic glutamate receptors in alcohol's reinforcing effects. Role: Dr. Crews, Co-PI, was involved in molecular signaling processes associated with the behaviors studied.

PHS Fellowship Supplemental Form

OMB Number: 0925-0002

A. Application Type:

From SF424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated here for your reference as you provide the responses that are appropriate for this Fellowship application.

☐ New ☒ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

B. Research Training Plan

1. Introduction to Application *(for RESUBMISSION applications only)*	Smith_NRSA_IntrotoResubmission_11_	Add Attachment	Delete Attachment	View Attachment
2. * Specific Aims	CSmith_NRSA_Specific_Aims_11_28_10	Add Attachment	Delete Attachment	View Attachment
3. * Research Strategy	CSmith_NRSA_ResearchStrategy_11_28	Add Attachment	Delete Attachment	View Attachment
4. Inclusion Enrollment Report *(for RENEWAL applications only)*		Add Attachment	Delete Attachment	View Attachment
5. Progress Report Publication List *(for RENEWAL applications only)*		Add Attachment	Delete Attachment	View Attachment

Human Subjects

Please note. The following item is taken from the Research & Related Other Project Information form. The response provided on that page, regarding the involvement of human subjects, is repeated here for your reference as you provide related responses for this Fellowship application. If you wish to change the answer to the item shown below, please do so on the Research & Related Other Project Information form; you will not be able to edit the response here.

Are Human Subjects Involved? ☒ Yes ☐ No

6. * Human Subjects Involvement Indefinite?	☐ Yes	☒ No	
7. Clinical Trial?	☐ Yes	☒ No	
8. Agency-Defined Phase III Clinical Trial?	☐ Yes	☐ No	

9. Protection of Human Subjects	Smith_DelDiscNRSAHumanSubjects_11_	Add Attachment	Delete Attachment	View Attachment
10. Inclusion of Women and Minorities	SmithWomenMinorities1002900304.pdf	Add Attachment	Delete Attachment	View Attachment
11. Targeted/Planned Enrollment	SmithTargetedPlannedEnrollmentTabl	Add Attachment	Delete Attachment	View Attachment
12. Inclusion of Children	SmithChildren1002900306.pdf	Add Attachment	Delete Attachment	View Attachment

Other Research Training Plan Sections

Please note. The following item is taken from the Research & Related Other Project Information form. The response provided on that page, regarding the use of vertebrate animals, is repeated here for your reference as you provide related responses for this Fellowship application. If you wish to change the answer to the item shown below, please do so on the Research & Related Other Project Information form; you will not be able to edit the response here.

Are Vertebrate Animals Used? ☐ Yes ☒ No

13. * Vertebrate Animals Use Indefinite?	☐ Yes	☒ No		
14. Vertebrate Animals		Add Attachment	Delete Attachment	View Attachment
15. Select Agent Research		Add Attachment	Delete Attachment	View Attachment
16. Resource Sharing Plan		Add Attachment	Delete Attachment	View Attachment
17. * Respective Contributions	CSmithRespectiveContributions10029	Add Attachment	Delete Attachment	View Attachment
18. * Selection of Sponsor and Institution	CSmith_NRSA_Selection_of_Sponsor_1	Add Attachment	Delete Attachment	View Attachment
19. * Responsible Conduct of Research	CSmithNRSAResponsibleConductofRese	Add Attachment	Delete Attachment	View Attachment

PHS Fellowship Supplemental Form

C. Additional Information

Human Embryonic Stem Cells

1. * Does the proposed project involve human embryonic stem cells? ☐ Yes ☒ No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s), using the registry information provided within the agency instructions. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the Registry will be used:

☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s):

Fellowship Applicant

2. Alternate Phone Number: 919-428-6228

3. Degree Sought During Proposed Award:

Degree:	If "other", please indicate degree type:	Expected Completion Date (month/year):	
PHD : Doctor of Philosophy		05/2014	Reset Entry

4. * Field of Training for Current Proposal: 2810 Behavioral Neuroscience

5. * Current Or Prior Kirschstein-NRSA Support? ☒ Yes ☐ No

If yes, please identify current and prior Kirschstein-NRSA support below:

* Level	* Type	Start Date *(if known)*	End Date *(if known)*	Grant Number *(if known)*	
Predoctoral	Institutional	07/01/2009	06/30/2010	T32DA007244	Reset Entry
Predoctoral	Institutional	08/01/2010	07/31/2011	T32DA007244	Reset Entry
					Reset Entry
					Reset Entry

6. * Applications for Concurrent Support? ☐ Yes ☒ No

If yes, please describe in an attached file: Add Attachment | Delete Attachment | View Attachment

7. * Goals for Fellowship Training and Career: GoalsforFellowshipTrainingandCar — Add Attachment | Delete Attachment | View Attachment

8. * Activities Planned Under This Award: SmithActivitiesplannedunderthisa — Add Attachment | Delete Attachment | View Attachment

9. Doctoral Dissertation and Other Research Experience: CSmith_DoctDisserOtherResExp_11_ — Add Attachment | Delete Attachment | View Attachment

10. * Citizenship:
☒ U.S. Citizen or noncitizen national
☐ Permanent Resident of U.S. Pending
☐ Permanent Resident of U.S.
(If a permanent resident of the U.S., a notarized statement must be provided by the time of award)
☐ Non-U.S. Citizen with temporary U.S. visa

PHS Fellowship Supplemental Form

C. Additional Information (continued)

Institution

11. ☐ Change of Sponsoring Institution

Name of Former Institution:

D. Budget

All Fellowship Applicants:

1. * Tuition and Fees:

☐ None Requested ☒ Funds Requested:

Year 1	8,940.00
Year 2	9,745.00
Year 3	10,621.00
Year 4	
Year 5	
Year 6 *(when applicable)*	
Total Funds Requested:	29,306.00

Senior Fellowship Applicants Only:

2. Present Institutional Base Salary: Amount | Academic Period | Number of Months | Reset Entry

3. Stipends/Salary During First Year of Proposed Fellowship:

a. Federal Stipend Requested: Amount | Number of Months

b. Supplementation from other sources: Amount | Number of Months

Type (sabbatical leave, salary, etc.)

Source

E. Appendix

Add Attachments | Delete Attachments | View Attachments

Tracking Number:GRANT10752798 Funding Opportunity Number:PA-10-108 Received Date:2010-12-02T09:53:38-04:00

To the Reviewers: Thank you for carefully reviewing my initial F31 Application. Scores from the previous review are summarized to the right. Any weaknesses mentioned are noted below with the reviewer (R1, R2, and R3) who noted the weakness, a response, and the location of any applicable changes in the application. All changes in the application are denoted by *modified font* and a vertical line in the left margin.

Reviewer	R1	R2	R3
Applicant	3	2	4
Sponsors	3	3	5
Res. Plan	6	3	2
Train. Pot.	4	5	1
Environ.	3	1	1

Applicant: Applicant's research productivity (R1 & R3): The applicant currently has manuscripts in preparation (*Doctoral Dissertation and Other Research Experience*). Concern about UNC grades (R2): UNC grading scale clarified (P=B or better; *Applicant Biosketch*).

Sponsor: Dr. Boettiger is junior and lacks mentoring experience (R1, R2 & R3): added senior Co-Sponsor, Dr. Fulton Crews (*Training Plan; Biosketch; Letter of Support*). Lack of NIH support, external funding (R2 & R3): Sponsor is actively pursuing extramural support (*Sponsor Biosketch*), Sponsor's start-up funds and K-award funds will be sufficient to fund the proposed studies without external funding (*Training Plan*). Lack of sufficient experience in structural MRI and DTI methods proposed in Aim2 (R1): The original Aim 2 studies have been eliminated from the proposal; all studies now focus on fMRI, in which the Sponsor is adequately trained (*Research Training Plan*). Supplemental Mentors for Training (R3): the applicant has formed his dissertation committee, which includes Dr. Crews, Dr. Weili Lin, a neuroimaging expert , Dr. Regina Carelli, a noted expert in the neurobiology of learning and addiction, and Dr. Gabriel Dichter, an expert in neuroimaging of human neurodevelopmental disorders (*Training Plan)*. The applicant will meet with this committee biannually beginning Jan 2011. All members of the committee are accessible for individual meetings as needed (Training Plan).

Research Training Plan: Concern about hypotheses for Aim 1 (R1): Hypotheses and supporting arguments have been clarified (Research Strategy). Lack of detail for structural MRI and DTI aim (R1): aim removed from proposal (*Specific Aims*) to allow for focus on fMRI image analysis training with sMRI and DTI as future directions to investigate effects of age and alcohol use (*Research Strategy*). Generality of Aim 3 (now Aim2) (R1): Aim modified to investigate adults (ages 25-40); hypotheses now more clearly specified. (*Research Strategy*). Lack of clarity regarding behavioral vs. BOLD analyses (R1): Data analysis procedures clarified (Research Strategy). Justification for age group specification not made clear (R2): Aim 1 modified to compare 18-23 year olds with 25-40 year olds, age groups between which we observed the largest behavioral differences in our pilot data (*Research Strategy*). Lack of multimodal approach to analysis of brain data (R2): While the sMRI and DTI Aim has been eliminated, these data will be collected; however to limit the scope of the application, multimodal and connectivity-based analyses are included as future directions (Research Strategy). Lack of Innovation section (R2): not required in F31 application (PA-10-108, Section IV.6). Clarification of participant exclusion criteria (R2): individuals who have never consumed alcohol will be excluded (*Human Subjects*). Necessity of funding for training plan (R3): collecting fMRI data for the proposed number of subjects will require lab funds to be allocated away from tuition and stipend support for the applicant, which NRSA support would help offset

Training Potential: Lack of sufficient training for structural and diffusion image analysis in Aim 2 (R1): Original Aim 2 eliminated (*Specific Aims*); Dr. Lin as a member of the applicant's dissertation committee will be a resource for undertaking these analyses as future directions of the current proposal (*Research Strategy*). Lack of manuscript prep in early training (R2): manuscripts with the applicant as first author are currently in preparation (*Doctoral Dissertation and Other Research Experience*). Lack of training in human brain development (R2): coursework added to address this weakness (*Activities Planned under Award*).

Institutional Environment and Commitment to Training: Funding for the scanning sessions (R1): Sponsor's start-up funds and K-award funds will be sufficient to fund the proposed studies (*Training Plan*).

2. SPECIFIC AIMS

Late adolescents/young adults (ages *18-23*) are the group at greatest risk for developing an alcohol use disorder (AUD) (Kandel and Logan, 1984; Brown et al., 2008), possibly due in part to their greater impulsiveness. The decline in heavy alcohol use that typically occurs in the mid-twenties may reflect a maturational process (Kandel and Logan, 1984), as the structural development of frontal structures implicated in self-regulation is complete around the early-to-mid twenties (Giedd, 2004; Hooper et al., 2004; Rubia et al., 2006; Eshel et al., 2007). *Furthermore, recent work suggests that adolescents (mean age: ~16) are more sensitive to appetitive cues than are adults (mean age: ~24) due, perhaps, to increased activity in the ventral striatum (Somerville et al., 2010). Moreover, adolescents may be more sensitive to immediate over long-term gains due to earlier maturation of subcortical structures (striatum, nucleus accumbens) relative to frontal structures over this period of development (Galvan et al., 2006; Somerville and Casey, 2010).* While late adolescents are widely regarded as impulsive (Chambers and Potenza, 2003; de Wit, 2009), little work to date has used quantitative, objective measures of impulsiveness, such as those yielded by delay-discounting tasks, to assess developmental changes from late adolescence to early adulthood, *particularly between the ages of 20 and 30.* One recent study reports a significant decline from childhood to adulthood in the tendency to choose immediate ("*Now*") over delayed ("*Later*") rewards (Olson et al., 2007), yet the differences between late adolescents and adults in *Now*/*Later* decision making remained unexplored. We addressed this gap using a delay discounting task optimized for neuroimaging and known to engage the frontal lobes (Boettiger et al., 2007). Our preliminary data (see *Approach*) show that late adolescents *(ages 18-23)* choose *Now* over *Later* significantly more often than do adults (ages *25-40*); this age-related decrease in impulsive choice is *l*ess pronounced in *heavy drinking adults*. We now propose to investigate the neurobiological bases of these behavioral differences. The proposed studies will provide a better understanding of the developmental changes that occur in brain areas governing *Now/Later* decision making and will inform future prospective studies of the impact of drinking on late-adolescent/early adult brain development.

The *long-term goal* of this line of research is to ascertain the nature of late adolescent changes in the function of frontal circuits engaged during *Now*/*Later* decision making and whether heavy alcohol use is associated with perturbations in such changes. The *overall objective* of this application is to use fMRI to compare the brain areas engaged during *Now*/*Later* decision-making between late adolescents and adults, and to determine whether heavy alcohol use is associated with abnormalities in normal age-related differences in these neural circuits. Our *central hypothesis* is that immaturity in frontal circuit function and increased relative signaling in striato-limbic subcortical structures promote impulsive decision making in late adolescents. In addition, we hypothesize that the brains of heavy drinking adults will display functional similarities to those of late adolescents, suggesting that heavy drinking is associated with impaired development of frontal brain structures, which may promote impulsive decision making. We will test our central hypothesis by pursuing the following *specific aims*:

Aim 1. Indentify functional differences in frontostriatal circuits associated with *Now/Later* decision making in late adolescents versus adults.

Our *working hypothesis* is that adults will activate the orbitofrontal cortex (OFC) to a greater degree when making *Now/Later* decisions, which is typically associated with *Later* preference (Boettiger et al., 2007), while late adolescents will show relative hyperactivity in subcortical striato-limbic structures *such as the ventral striatum/nucleus accumbens implicated in increased sensitivity to immediate rewards in this age group (Galvan et al., 2006; Somerville and Casey, 2010).* Our *expected outcomes* for Aim 1 are to identify functional neural correlates of age-related differences in behavior. These outcomes are expected to have an important *positive impact* because they will uncover neural bases of late adolescents' impulsiveness that may contribute to their elevated risk for AUDs.

Aim 2. Determine whether the impulsive decision-making observed in heavy drinking adults is associated with signs of functional immaturity in frontal circuits.

Our *working hypothesis* is that heavy drinking will be associated with functional immaturity in frontal cortical structures integral in cognitive control and behavioral inhibition (OFC, dorsal prefrontal cortex) *(Miller and Cohen, 2001)*. Our *expected outcomes* for Aim 2 are to ascertain the functional neural correlates of impulsive decision making in *heavy drinking adults*. These outcomes are expected to have an important *positive impact* because they will *identify differences in brain function associated with risky alcohol use and which underlies maladaptive decision-making, which could contribute to the establishment of alcohol use disorders.*

The findings from this research plan will provide a better understanding of the development of neural circuits governing *Now/Later* decision making (Aim 1). This research will also provide insight into the association between drinking behavior and the function of neural circuits engaged by *Now/Later* decision making, which may sustain impulsivity into adulthood and contribute to the development and/or maintenance of AUDs (Aim 2).

3. RESEARCH STRATEGY

3a. Significance

In adults, a greater tendency to choose immediate over delayed rewards is associated with addictive disorders (Reynolds, 2006). Existing data suggest that discounting of delayed rewards normally decreases from childhood to the early 30's (Green, 1994; Green et al., 1996; Scheres et al., 2006; Olson et al., 2007). However, little work to date has investigated the developmental trajectory from late adolescence to early adulthood of discounting behavior or its underlying neural substrates. Heightened discounting of delayed rewards in late adolescence could contribute to the increased risk for AUDs at this life-stage (Kandel and Logan, 1984; Brown et al., 2008). We compared the delay discounting of late adolescents and adults in an fMRI-compatible delay discounting (*"Now/Later"*) task. Our preliminary data demonstrate that late adolescents (*ages 18-23*) choose smaller, immediate rewards ("*Now*") significantly more often than do adults (*ages 25-40*; see *Approach*). We now propose to investigate the underlying neural bases of this age-dependent change in decision-making behavior.

Although the underlying neural bases of the age-related behavioral differences that we observed are unknown, some evidence points to developmental maturation of the frontal lobes. First, the development of frontal structures remains incomplete until the early-to-mid twenties (Sowell et al., 1999; Casey et al., 2000; Sowell et al., 2001; Giedd, 2004; Gogtay et al., 2004; Lenroot and Giedd, 2006), consistent with our observed decrease in delay discounting around age *24*. Second, fMRI data from adults using the same *Now/Later* task found that activity in two frontal structures, the dorsal prefrontal cortex (dPFC) and orbitofrontal cortex (OFC), predicts choice behavior in this task (Boettiger et al., 2007). These data are consistent with models suggesting a role for the dPFC in cognitive control (Miller and Cohen, 2001) and for the OFC in encoding value of choice outcomes (Wallis, 2007).Thus, developmental changes in these areas would be expected to alter choice behavior. Finally, a study of individuals aged 9-23 found that age-related increases in frontal white matter integrity are positively correlated with preference for larger, delayed rewards (Olson et al., 2009). As this latter study included only seven (of 79) individuals ages 22-23, no conclusions can be drawn with regard to white matter changes from late adolescence to early adulthood. However, Olson et al.'s findings do not refute our hypothesis that maturation of frontal structures underlies the decline of *Now* preference in early adulthood.

In addition to the age-related differences in *Now/Later* decision making described above, we found that *heavy drinking adults (AUDIT consumption scores ≥ 6)* choose immediate rewards *significantly more often than do lighter drinking adults* (see *Approach*). We speculate that this behavioral immaturity reflects immaturity in frontal function, which may persist in heavy drinkers, as either a cause or a consequence of harmful drinking. It is known that frontal circuits are especially prone to insult by heavy alcohol consumption, especially at binge levels (De Bellis et al., 2005; Miguel-Hidalgo et al., 2006; Jacobus et al., 2009; McQueeny et al., 2009). Moreover, decreased metabolic activity has been observed in the PFC and OFC of abstinent alcohol abusers (Volkow et al., 1997; Catafau et al., 1999), suggesting that heavy alcohol use may impair frontal structures crucial for *Now/Later* decision making. This is consistent with the Sponsor's findings of heightened discounting of delayed rewards in abstinent alcoholics associated with differences in dPFC and OFC activation during *Now/Later* decision-making (Boettiger et al., 2007). Thus, the brain regions that predict behavior in our *Now/Later* task and whose maturation into early adulthood may explain the age-dependent decline in discounting of delayed rewards from late adolescence to early adulthood are also structures in which dysfunction is linked to AUDs (Verdejo-Garcia et al., 2007; Clark et al., 2008; Yeh et al., 2009). We expect that our proposed studies will provide new insight into the neurobiology underlying an important form of decision-making and whether heavy alcohol use is associated with abnormal development of function in brain areas underlying this behavior. *This contribution is significant because it will address the unanswered question of whether frontal circuit maturation can explain the shift in Now/Later decision making that occurs in early adulthood. Furthermore, a closer investigation of the neural underpinnings of late adolescent vs. adult decision making and the interaction of drinking behavior with age will provide further means to understand at a behavioral neuroscience level why late adolescents are at an increased risk for developing AUDs (Kandel and Logan, 1984; Brown et al., 2008; Squeglia et al., 2009).*

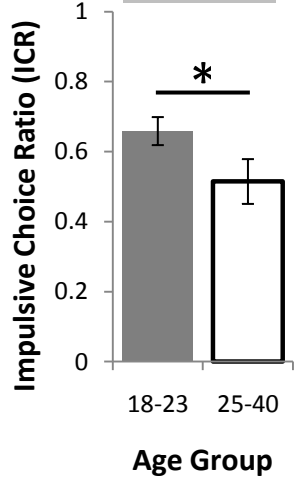
c. Approach.

Aim 1. Indentify functional differences in frontostriatal circuits associated with *Now/Later* decision making in late adolescents versus adults.

Introduction. While late adolescents are at increased risk of engaging in maladaptive behaviors, such as problem alcohol use (Crews and Boettiger, 2009; Ernst et al., 2009), we currently lack a complete understanding of the neurobiological bases of such risk. Possible contributors to maladaptive behaviors in late adolescents are differences in decision making processes. The *objective of this aim* is to determine functional brain differences underlying behavioral differences in the tendency to choose immediate ("*Now*") over delayed ("*Later*") rewards observed among late adolescents (*age 18-23*) relative to adults (*age 25-40*). To achieve this aim, we will test the *working hypothesis* that adults activate the OFC to a greater degree when making *Now/Later* decisions than do late adolescents, as high OFC activity during *Now/Later* decisions is typically associated with *Later* preference in adults (Boettiger et al., 2007). In contrast, we predict that late adolescents will show greater activity in reward and limbic associated regions (ventral striatum, nucleus accumbens, and amygdala) during *Now/Later* decision-making relative to adults. *This hypothesis is motivated by recent work suggesting the adolescents and young adults (ages 14-17) are more approach oriented, and thus more sensitive to reward, than adults (ages 22-30) in a task measuring risk taking behavior (Cauffman et al., 2010).* We will test our working hypothesis by comparing brain activity during *Now/Later* decision-making between late adolescent and adult groups using fMRI. The *rationale* for this aim is that improved understanding of the neural bases of changes in decision making behavior from late adolescence to adulthood may stimulate new strategies to prevent alcohol use disorders (AUDs). Furthermore, identifying brain structures that are differentially engaged during *Now/Later* decisions between late adolescents and adults may identify additional regions of interest (ROI) for investigation in future structural imaging studies. Such findings will be of importance because they will enhance our understanding of how brain maturation from late adolescence to adulthood may contribute to age-dependent changes in decision-making behavior.

Justification and Feasibility. Our approach requires that we be able to reliably measure immediate reward bias, particularly in the context of fMRI. Second, it requires that we are able to adequately collect and analyze fMRI data. The following preliminary data support the feasibility of the proposed approach. First, the Sponsor has developed an fMRI compatible *Now/Later* task that reliably detects differences in the decision-making of adults with versus without a history of alcoholism (Mitchell et al., 2005; Boettiger et al., 2007; Mitchell et al., 2007). A previous fMRI study of this task found that that activity in the OFC during decision-making is negatively correlated with the tendency to choose *Now* over *Later* (i.e. with "immediate reward bias") (Boettiger et al., 2007). This task was also used successfully by the Sponsor in a second fMRI study (Boettiger et al., 2009). Thus, our proposed use of this task during fMRI is feasible. Second, in a preliminary behavioral study, *we tested the Now/Later decision-making of 80 subjects (n=46 late adolescents (mean age: 20.3±1.5) and n=22 adults (mean age: 31.6±4.3) with no substance abuse history, no DSM-IV alcohol dependence symptoms, and low to moderate levels of alcohol consumption (AUDIT consumption score < 6). Using immediate reward bias (ICR; see below) as the dependent measure and including gender and socioeconomic status as covariates, we found a significant effect of age on ICR (F (1, 60)=4.05,p<0.05; Fig. 1, right),* with late adolescents choosing immediate rewards significantly more often than do adults**.** We *hypothesize* that these results reflect immaturity of frontal circuits in late adolescents (Paus et al., 2001; Gogtay et al., 2004; Sowell et al., 2004; Yurgelun-Todd, 2007; Giedd, 2008; Shaw et al., 2008) and expect to find differences in frontal activity underlying Now/Later decision-making that correlate with these behavioral differences. Beyond motivating the proposed studies, our preliminary data demonstrate our ability to recruit participants in the proposed age ranges.

Figure 1



Research Design.

Overview: This study will investigate the differences in brain activity underlying *Now/Later* decision-making between late adolescents (*age 18-23*) and adults (*age 25-40*).

General Methods

Consent/screening: Subjects will be thoroughly screened for inclusion/exclusion criteria (see *Human Subjects*). *In brief, exclusion criteria will include lack of a high school diploma or GED, non native English speakers, history of neurological disease, use of psychoactive medications, those meeting DSM-IV criteria for alcohol dependence or any other*

substance use disorder, nondrinkers, and those with contraindications to fMRI. Individuals younger than 18 and older than 40 years of age will also be excluded from participation in the study.

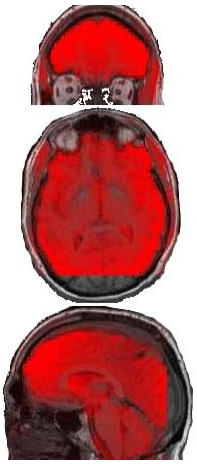
Questionnaires: To identify factors accounting for individual differences, participants will complete standardized questionnaires. These will quantify drug and alcohol use (DDQ, RAPI, DUSI, AUDIT*, AUQ binge drinking score*) (Collins et al., 1985; White and Labouvie, 1989; Tarter, 1990; Saunders et al., 1993; *Townshend and Duka, 2005)* family history of alcohol abuse (FTQ; Mann et al., 1985), affect (Spielberger, 1985; Beck and Steer, 1987; McNair et al., 1992), and personality traits (FTPI, LOC, APS, BIS) (Wallace, 1956; Rotter, 1966; Butcher JN et al., 1990; Barratt, 1994). We will also collect estimates of IQ (SILS; Zachary, 1991) and socio-economic status (SES; Hollingshead, 1975).

Delay discounting (Now/Later) task: This task is described in detail elsewhere (Boettiger et al., 2007). In brief, participants select between hypothetical reward pairs, each a dollar amount at a point in time; we refer to these two alternatives as "*Now*" and "*Later*". The *Later* amount and delay time vary across trials, as does the percentage difference between *Now* and *Later*. *Now* is always a lesser amount available "TODAY". Immediate reward bias is calculated as a ratio of *Now* choices relative to total number of subjective choices made, termed the impulsive choice ratio (ICR). *In addition, our task includes two control (CON) conditions, "SOONER" and "LARGER", in which participants select the correct response based on the instruction cue (i.e, the sooner or larger option). This allows us to assess the accuracy of responses and also serves as an important control in our fMRI analyses, by capturing activity associated with objective (CON), rather than subjective choice (WANT).*

Subjects will be healthy males and females (ratio: 50:50), *n=20* per age group (18-23 and 25-40; total *n=40*).

Functional Magnetic Resonance Imaging: Participants will perform the *Now/Later* task within a 3T MR scanner (see *Facilities* and *Equipment*) while we obtain continuous whole-brain blood-oxygen-level-dependent signal. A high-resolution anatomical image will also be obtained for each subject. Beginning with postdoctoral training, the Sponsor has acquired considerable experience with this technique, resulting in publications in high level journals. The proposed methods are similar to those used previously by the Sponsor in studies of *Now/Later* decision-making (Boettiger et al., 2007; Boettiger et al., 2009), with minor adjustments to accommodate scanner differences*. Preprocessing of the data, including motion correction, will follow the same procedure described in Boettiger et al., 2007, with necessary adjustments for the transition from SPM2 to SPM8*. Here, we briefly review these adjustments. The following parameters will be used to acquire T2*-weighted single shot gradient echo echoplanar images (EPI): TR=2sec, TE=*27*ms, Flip Angle 80°, FOV=22.4 cm in a 64x64 matrix, *40* interleaved coronal slices (3.5 mm^2 in plane, 4 mm between plane resolution). *Each acquisition will be preceded by 5 dummy gradient RF pulses to achieve steady state tissue magnetization and minimize startle-induced motion.* These parameters produce whole brain coverage for most participants; when it does not, the occipital pole will be excluded, as our hypotheses do not involve early visual cortex. These parameters were selected to generate adequate coverage for the OFC, dPFC, and anterior temporal lobe (Deichmann et al., 2003; Weiskopf et al., 2006; Du et al., 2007). Fig. 2 (right) depicts mean EPI coverage for one subject using the proposed parameters on the BRIC's *Trio* 3T *overlaid on that subject's high-resolution structural image*. As shown, coverage appears adequate for the proposed studies.

Figure 2



Hypothesis. Activity in frontal and subcortical structures will vary across age group with adults (*25-40*) showing greater activity in the OFC and late adolescents (*18-23*) demonstrating greater activity in subcortical structures such as the amygdalae and ventral striatum.

Statistical Analyses. With ICR as the dependent measure, we will use an ANOVA to test for a significant main effect of age group. *Gender and SES will be included as covariates in the model to control for potential confounding factors.* An *a priori* power analysis indicates that a sample size of *n=40* has 90% power to detect a moderate effect size (*0.52*). As our preliminary behavioral study has found a moderate (*>0.55*) effect of age, we anticipate that this study will be adequately powered with *20* subjects per group, even if effect sizes are smaller than expected. *For our BOLD data, we will generate contrasts of [WANT-CON] conditions to identify brain activity associated with subjective decision-making.* Within subjects, we will define ROI *a priori* based on our past studies (Boettiger et al., 2007; Boettiger et al., 2009). *[WANT-CON] contrast differences* within these ROI will be assessed via the same type of ANOVA. Additional exploratory mapwise analyses will seek to identify brain areas in which activity during *Now/Later* decisions shows main effects of *age group*.

Expected Results & Interpretation. We expect that during *Now/Later* decision-making, adults will engage the OFC to a greater extent than will late adolescents and that the degree of activation will be negatively correlated with our behavioral measure of immediate reward bias (ICR). Additionally, we expect that late adolescents will show greater activation in subcortical impulse-related structures such as the amygdalae and ventral striatum, and that the degree of activation in these structures will positively correlate with ICR.

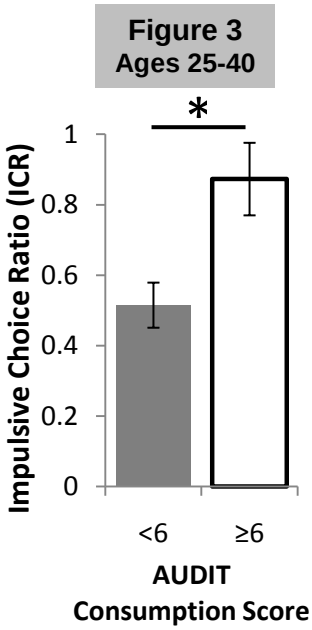
Time to complete study. See *Timeline*.

Expected Outcomes. This fMRI study will allow us to better understand the role of brain maturation in age-dependent differences in immediate reward bias. In particular, we will be able to identify structures and circuits which function differently in late adolescents versus adults during *Now/Later* decision-making. Such findings will improve our understanding of the neural mechanisms of impulsive decision making and may provide neurobiological insight into why late adolescents tend to be more impulsive than adults.

Potential Problems & Alternative Strategies. It is possible that we will not be able to detect age-related differences in brain activity during *Now/Later* decision-making. Analyzing our participant groups with gender as an independent variable *could* increase our age effect signal as it is known that the time course of brain development differs between males and females (Lenroot et al., 2007; Lenroot and Giedd, 2010). *Furthermore, a significant negative correlation between age and ICR has been observed in our preliminary behavioral experiments ($r = -0.298$, $p<0.005$), allowing for the possibility of using age as a continuous variable in regression analyses of the mean parameter estimates in our ROI, as well as exploratory mapwise analyses.*

Aim2. ***Determine whether the impulsive decision-making observed in heavy drinking adults is associated with signs of functional immaturity in frontal circuits.***

Introduction. Although it is known that abstinent alcoholics choose *Now* more frequently in our task than do control subjects (Mitchell et al., 2005), and our preliminary data suggest that late adolescents are also more likely to choose *Now* over *Later*, investigating the relationship between alcohol use and functional brain immaturity is lacking. The *objective of this aim* is to determine if heavy alcohol use is associated with differences in frontal circuit function and more impulsive decision making *in individuals with no current or past DSM-IV alcohol dependence*. To achieve this aim, we will test the *working hypothesis* that heavy drinking is associated with functional immaturity in frontal cortical structures engaged during *Now/Later* decision-making. The *rationale* for this aim is to assess whether *heavy alcohol consumption* might impair developmental maturation of frontal structures, which could contribute to the larger immediate reward bias observed among abstinent alcoholic adults relative to age-matched controls. The findings from this experiment will be useful in determining whether future prospective studies of the impact of drinking behavior on late-adolescent brain development are warranted.



Justification and Feasibility. Previous research suggests that the frontal structures engaged during our delay discounting task (Boettiger et al., 2007) are more sensitive to the neurodegenerative effects of alcohol than any other part of the brain (Corso et al., 1998; De Bellis et al., 2005; Miguel-Hidalgo et al., 2006). Thus, we expect to observe a relationship between immediate reward bias, OFC and PFC function, and degree of alcohol consumption.

Using the Alcohol Use Disorders Identification Test (AUDIT) to group participants into *heavy drinkers (AUDIT consumption score ≥ 6) or low/moderate drinkers (AUDIT consumption < 6)*, a preliminary behavioral study (see Aim 1, *Justification and Feasibility*) revealed *a main effect of alcohol consumption on ICR ($F_{(1,92)}=10.923$, $p=0.001$). In addition, a near-significant age by AUDIT consumption interaction was found ($F_{(1,92)}=3.834$, $p=0.053$), which was due to the fact that age effects on decision-making differed between moderate and heavy drinkers. Among moderate drinkers ($n=68$), adults chose less impulsively than did late adolescents ($t_{66}=2.104$, $p<0.05$). In contrast, among heavy drinkers ($n=45$), this age-dependent decline in ICR was not observed. In fact, among heavy drinkers, we found a trend toward* ***increasing*** *ICR with age ($t_{28}=1.894$, $p=0.069$); mean ICR was significantly higher among heavy drinking adults relative to low/moderate drinking adults ($t_{27}=4.452$, $p<0.001$; Figure 3, above right).* Thus, *heavy alcohol use in adults with no past or present alcohol dependence* is associated with high immediate reward bias in our *Now/Later* task, similar to that observed in late adolescents and abstinent

alcoholics. These preliminary data demonstrate that we will be able to recruit the target populations for the proposed studies.

This Aim will involve the same experiments outlined for Aim 1 with the addition of a subclinical heavy drinking population, which we will compare to moderately drinking adult participants. We will conduct the experiments of Aim 2 concurrently with Aim 1, although it will provide results independent of that Aim that may provide insight into neural factors mediating the interaction between alcohol use and age on immediate reward bias.

Research Design.

Overview. This study will investigate functional differences in frontostriatal circuits associated with heightened immediate reward bias in heavy alcohol users.

See Aim 1 above for General Methods

Subjects: A key difference in the experiments associated with this Aim is that the subjects *will be restricted to the 25-40 age group and will include individuals with AUDIT consumption scores ≥ 6*, which is indicative of heavy, binge-like drinking behavior. Subjects meeting DSM-IV criteria for current or past *alcohol dependence* will be excluded. The same fMRI data will be collected from these subjects, and the same analyses will be performed, replacing the factor of age with alcohol use group. The value of this aim is that we will be able to investigate the impact of *heavy, at-risk* drinking behavior on immediate reward bias and the function of frontal structures involved in immediate reward bias.

Hypothesis. We hypothesize that *heavy drinking* adults will display immediate reward bias *greater than that of low to moderate drinking adults*, that *this similarity in immediate reward bias of heavy drinking adults to late adolescents* will be reflected in equivalent functional immaturity in the frontostriatal circuits of adult problem drinkers and late adolescent controls.

Statistical Analyses. *With ICR as the dependent measure, w*e will use ANOVA to test for a *main effect of alcohol use*. Power analysis as for Aim 1. We *will include the moderate drinking adult population from Aim 1 in this study*. Thus, we will need to recruit *20 additional* adults (*50%* female) with *AUDIT consumption scores ≥ 6* to be combined with control subject data collected in Aim 1 for a total of *40 subjects*. *D*ata collection for both Aims will be concurrent. *Within subjects, we will define ROI a priori based on our past studies (Boettiger et al., 2007; Boettiger et al., 2009). Additional ROI may be defined based on the findings of Aim 1. Mean parameter estimates within these ROI will be assessed via the same type of ANOVA. Additional exploratory mapwise analyses will seek to identify brain areas in which activity during Now/Later decisions shows a main effect of alcohol use.*

Expected Results & Interpretation. We expect to find effects of alcohol use reflected in frontostriatal activity during Now/Later decision-making. Our preliminary behavioral study suggests that we will observe an effect of *heavy drinking* on our measure of immediate reward bias. Thus in the proposed study we will collect detailed information on alcohol use, such that we can characterize what types of drinking behavior (*e.g.* binge drinking *(Stephens and Duka, 2008; Scaife and Duka, 2009)*) are associated with high immediate reward bias and *abnormal adult function* in frontostriatal circuits.

Time to complete study. See *Timeline*.

Expected Outcomes. We expect the results from this Aim to provide us with insight into the neural mediators of the relationship between heavy alcohol use and immediate reward bias. Particularly, we hope to identify the role of frontostriatal circuit functional maturation in immediate reward bias and how *heavy alcohol intake* may negatively impact components of these circuits. If we can determine the effect of alcohol use on frontostriatal function and the behavioral consequences of this effect on *Now/Later* decision making, we may be able to better understand the increased risk for AUDs *associated with heavy drinking (Courtney and Polich, 2009)*.

Potential Problems & Alternative Strategies. We expect to see differences between *heavy and moderate drinkers* in terms of behavior (immediate reward bias) and neurobiology (circuits engaged during Now/Later decision-making). However, heterogeneity in drinking behavior within groups may make interpreting the relationship between alcohol and our dependent measures difficult. Thus, an extensive battery of drinking measures will be collected from our subjects (see *Human Subjects*) such that we can *more accurately group participants for analysis, or use regression analyses based on continuous measures.* It may be necessary to follow-up this initial data collection approach with a more targeted recruitment of participants with similar drinking behaviors using a variety of alcohol use measures for subject screening.

Timeline:

Project Year	Year 1				Year 2				Year 3			
NIH Quarter	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4
Scientific Proposal												
Aim 1: fMRI controls developmental study												
Data Collection	■	■	■	■	■	■						
Data Analysis		■	■	■	■	■	■	■				
Aim 2: fMRI alcohol use study												
Data Collection	■	■	■	■	■	■	■	■				
Data Analysis					■	■	■	■	■	■		
Career Development												
Didactic Courses	■	■	■	■								
Multidisciplinary Seminars	■	■		■	■	■		■	■	■		■
Workshops and Tutorials			■				■				■	
Professional Conferences		■	■			■	■			■	■	
Manuscript Preparation	■	■	■						■	■	■	■
Thesis Preparation & Defense									■	■		
Postdoctoral Interviews										■	■	
F32 submission											■	■

Future directions

Structural data will be obtained during the same scan sessions used to collect fMRI data for both Aims 1 and 2. We plan to use voxel based morphometry (VBM) analyses of high-resolution structural MRI (sMRI) data to assess age-related changes in gray matter density, using a strategy similar to that of Sowell et al. (1999). Our study, however, will concentrate on an age group not delineated in the Sowell study: late adolescents (18-21). In addition, we will collect diffusion tensor imaging (DTI) data with plans to investigate changes in white matter density and anisotropy as well as connectivity between structures of interest using an automated fiber tractography technique similar to that of Liston et al., 2006 (Liston et al., 2006). By collecting sMRI, DTI, and fMRI data, we plan to conduct multimodal and network-based analyses (Behrens and Johansen-Berg, 2005; Hagmann et al., 2007) of this dataset in the future to better delineate the role of structural and functional development of frontostriatal circuits, and possible disturbances in this development as a result of heavy drinking, in immediate reward bias behavior and the establishment of alcohol use disorders in adulthood (see (Lin et al., 2008; Gao et al., 2009) for examples of how a network approach to brain connectivity could be applied using techniques and tools available at UNC Chapel Hill).

Positive results in these studies would warrant a prospective study where the effects of problem alcohol use on frontostriatal structure and function and *Now/Later* decision making could be monitored within individuals from age 18 to 25. Such a study would be invaluable in understanding how problem alcohol use, especially during late adolescence, can result in neurobiological changes that increase the likelihood that such use could progress into an AUD that persists into adulthood. Thus, the proposed set of studies will provide a more complete understanding of the neurobiological bases of *Now/Later* decision making and how development and alcohol functionally impact these circuits. Such an understanding may eventually lead to improved treatments for those with AUDs.

8. HUMAN SUBJECTS

Human Subjects Involvement and Characteristics.

General inclusionary criteria for all subjects are that they be high school educated and medically healthy subjects aged 18-40. Due to difficulties in interpreting cognitive studies in subjects with English as a second language, only native-English speakers will be asked to participate in these studies. Participants will be selected in an unbiased fashion with respect to race and equal numbers of male and female participants will be recruited. Every effort will be made to insure that the subject population conforms to the NIH policy on Gender and Minority Inclusion in Research Study populations. Subjects will also be excluded if they have other known neurological disease such as dementia, seizures or head trauma; or known psychiatric disease such as depression or psychosis; or known systemic disease such as cancer, cardiovascular or inflammatory disease which could influence cognitive functioning. Subjects will be excluded if they have any type of motor or visual disturbance which precludes them from performing the cognitive tasks. We will also exclude individuals currently using psychoactive drugs (aside from moderate caffeine, alcohol, or nicotine), including prescription medications, or *individuals meeting DSM-IV alcohol dependence criteria as assessed by semi-structured interview based on the DSM-IV Criteria for Substance Use Disorders (DCSUD) worksheet. Additionally, administration of the Alcohol Use Disorders Identification Test (AUDIT) will determine whether subjects are classified as heavy, possible problem drinkers (AUDIT consumption score ≥ 6) or light/moderate drinkers (AUDIT consumption score < 6). Those indicating that they never drink alcohol (nondrinkers) will be excluded from the study.*

Neuroimaging Exclusion criteria Additionally, participants will be excluded from the *fMRI study* if they have any contraindications to MRI, including electrically, magnetically or mechanically activated implants (such as cardiac pacemakers), intracerebral vascular clips (surgically implanted metal clips in any blood vessels within the brain), other non-removable body metal, tattoos, or if they are pregnant or claustrophobic. Participants will also be excluded from MRI testing if they are left-handed, as previous research has shown that handedness may impact the localization of brain activity. All pregnant women will be excluded from participating.

Screening Procedures People who show initial interest in a study are contacted via phone or e-mail with a questionnaire containing items related to psychiatric and neurological health, medications, use of psychoactive substances, and the presence of contra-indicators for MR research such as metal in the body. Evidence of neurological or psychiatric illness *(including alcohol dependence)*, or current use of psychoactive medications or other chemicals (excluding moderate caffeine, alcohol or nicotine) will result in non-inclusion in the study. *Additionally, individuals indicating that they never drink alcohol* or the presence of contra-indicators for MR research (such as metal in the body or pregnancy) will result in non-inclusion in the study. After reading and signing an informed consent form, subjects are given a rapid urine test to screen for psychoactive drugs and a breathalyzer test to screen for alcohol use. Results of these screening tests are not written down, but positive results will exclude participants from further participation. Female participants are also provided with a urine early pregnancy test at that time.

Neuropsychological/Behavioral Testing The proposed behavioral experiments will take place in the testing facilities within the PI's lab on the UNC campus. After the on-site screening procedure described above, participants will receive a battery of standardized questionnaires, and receive training in the cognitive task(s).

Magnetic Resonance Imaging For MRI participants, cognitive testing will take place in the context of an fMRI study, which will take place at the UNC Biomedical Research Imaging Center (BRIC), located at the southern end of the UNC campus. Studies will be performed on a Siemens 3T Allegra (head-only) or 3T Trio (full-body) MR scanner (a single scanner will be used for each experiment). Subjects are verbally read the experimental instructions just prior to scanning. Throughout the duration of the MRI session, it is ensured that the participants are well and comfortable. Participant status is assessed after each scan and adjustments are made to ensure participant comfort as necessary.

For all proposed experiments, after testing is complete, the purposes and predictions of the research will be clearly explained to the participants and their questions will be answered.

Sources of Materials.

Research material: We will collect data during the delay discounting task and MRI scans. We will collect demographic information, including gender, age, ethnicity, education, and socio-economic status. Participants will also complete standardized behavioral inventories to quantify personal alcohol and drug use, family history of alcohol use, and personality measures that could impact our results.

Data collection: All data collected will be entered into databases and stored on password protected computers using only alphanumeric subject ID codes as identifiers. Below is a detailed description of how we will collect the data. All data are being collected specifically for the proposed research project.

Neuropsychological/Behavioral Testing Following completion of the screening procedures, participants will receive a battery of standardized neuropsychological inventories to complete. Participants will then receive training in the decision making task. Subjects will then be escorted to the BRIC and will complete the computerized delay discounting task during fMRI.

Functional Magnetic Resonance Imaging Measurement of decision making behavior will take place while participants are scanned at the UNC BRIC. Studies will be performed on a Siemens 3T Allegra (head-only) or Siemens 3T Trio (whole-body) MR scanner (a single scanner will be used for all scans within a given study). Subjects are verbally read the experimental instructions just prior to scanning. Throughout the duration of the fMRI session, it is ensured that the participants are well and comfortable. Participant status is assessed after each scan and adjustments are made to ensure participant comfort as necessary.

Access to individually identifiable private information will be limited to the PI and the sponsor's research team (all of whom have completed CITI training). All data collected from the computerized tasks will be stored on a computer in the sponsor's lab, with the only identifier attached to the data being subject ID code. All imaging data will be stored in password protected files on secure computers in the sponsor's lab or on the BRIC's secure server; imaging data will include no personal identifiers. Paper copies used to collect questionnaire data and demographic information will be kept in a locked file cabinet in the sponsor's lab, with subject number as the sole identifier. For each study, a separate file linking the subject ID codes with subject names will be kept on a password protected computer in the sponsor's lab until completion of the study.

Potential Risks.

Cognitive testing There are no known risks for injury associated with the neuropsychological/behavioral components of these cognitive studies. Other possible risks include frustration, boredom, or fatigue. Moreover, answering detailed questionnaires and participating in computerized cognitive tasks may make subjects anxious or uncomfortable. Based on our previous experience, it is extremely unlikely that participants will find these potential psychological risks extreme enough to end their participation.

Functional MRI studies Potential minor risks and discomforts are associated with MRI acquisition. No known health risks are associated with these types of MRI studies, although the MRI makes loud noises as it acquires data, which could affect a participant's hearing. The only significant risk associated with MRI is the presence of ferromagnetic materials. This is a noninvasive technique involving no catheterizations or injection of exogenous tracers. A great many patients have now undergone magnetic resonance studies without apparent harmful consequences. Radiofrequency power levels and gradient switching times used in these studies are within the FDA approved ranges. Subjects must lie still in the MRI scanner for approximately 90 minutes, which subjects may find uncomfortable. Some people may become claustrophobic while inside the magnet, although this is less common with the head-only system available for the proposed studies. A relative contraindication to MRI studies is pregnancy, as the risk of MRI to fetuses is unknown.

Questionnaire data collection Answering the questionnaires may make the subjects uncomfortable and could cause emotional distress.

Confidentiality Information collected for the purpose of this research study will be kept confidential as required by law. All copies of testing records and results will be kept in locked filing cabinets, in locked offices, or in password-protected computer files. All information will be accessible only to authorized personnel. Alphanumeric codes will be used on all data sheets and data files in place of names. No participants will be

individually identified in any report or publication about this study. No personal identifiers will be associated with any study data. Screening information from participants will be kept in a locked filing cabinet along with their consent forms. The information collected during the initial screening is not retained.

Privacy Telephone interviews will be conducted from the sponsor's laboratory or office space. All laboratory personnel have undergone the CITI ethics training for conduct of human subjects research. All neuropsychological and behavioral testing will occur in private testing rooms. No mailed or emailed materials or messages will include subject specific data.

There are no known financial or legal risks associated with participating in these studies.

Recruitment and Informed Consent.

All subjects will participate in the informed consent process. Participants will be familiarized with the protocol by the PI or qualified study personnel, including its risks and benefits, and informed consent will be documented according to the regulations governing human subject research at the University of North Carolina, Chapel Hill, which meet the standards of the NIH.

Recruiting Participants will be recruited through local IRB approved flyers and advertisements distributed in the local community. Potential subjects who respond to these advertisements will be contacted initially via telephone or email. If contacted via email, subjects will be called for an initial telephone screening to determine whether the subject meets our inclusion criteria. Secure web-based screening tools may also be employed. Those meeting study criteria based on initial screening, will be scheduled to come to the lab to participate.

Inclusion of Women and Minorities Every attempt will be made to recruit women and minorities, including posting advertisements at the Sonja Haynes Stone Center for Black Culture and History; the Lesbian Gay Bisexual, Transgender Office; the Student Union; the Carolina Women's Center; and the Medical Campus buildings.

Initial Telephone Screening Potential participants are first screened via telephone for eligibility. This process includes a complete explanation of the protocol procedures. At that time, a potential participant can decline to participate.

Obtaining Informed Consent Upon arrival to participate in testing, participants will read and have explained to them the informed consent form. Informed consent is obtained in a comfortable, private area in the sponsor's Lab. Participants' questions about the protocol will be thoroughly answered prior to obtaining consent, with no time limit to this procedure. Upon consent, the subject is free to withdraw that consent at any time, which will be emphasized to the subject. Consent will be obtained by approved study staff.

Waiver of written consent for telephone pre-screening We have obtained (or will obtain) a waiver of written consent for the initial telephone/web-based screening. This request derives from our need to conduct a health and medical history pre-screen in order to ensure that individuals who respond to our IRB approved recruitment efforts are eligible to participate in our research projects. The health screen is preparatory to our research and its sole purpose is to ensure that participants meet our inclusion/exclusion criteria. A screening procedure that is efficient for both volunteers and the research team is necessary. These studies have strict inclusion/exclusion criteria and the pre-screening efficiently provides information needed to determine eligibility. To require potential study participants to come to our lab for screening that can be done over the telephone or web would place an undue burden on potential participants. Our phone script includes elements of informed consent and explains to potential participants how their privacy will be protected. The potential subject is informed that they may stop the phone conversation at any time. The health and medical information documented during the telephone screen is not disclosed to other investigators. Screens from participants who are excluded are destroyed. Screens from participants who are included are kept in a locked filing cabinet along with their consent forms and other screening information.

Protections Against Risks.

Cognitive testing The computerized tasks will be explained thoroughly and practice sessions will be provided before starting the task to reduce potential anxiety. To address the risk of frustration, boredom or fatigue, subjects will be given brief rests or breaks as needed during testing. Although it is hoped that subjects

will complete each task in each session, subjects may choose to stop participating at any time during the cognitive testing.

Functional MRI studies To address the risks posed by contraindications to MRI, detailed routine screening will exclude pregnant individuals and those with non-removable metal in their body, pacemakers, tattoos, or nicotine patches, and all subjects will be carefully checked for metal prior to entering the magnet room. To reduce the incidence of claustrophobia while inside the magnet, people with a history of claustrophobia will be excluded and all subjects will be warned of this possibility. To protect subjects from the loud noises the scanner makes as it acquires data, while still permitting communication between the investigator and subject, subjects are provided with ear plugs and fitted with MR compatible headphones. Efforts will be made to make the subjects as comfortable as possible, and procedures will be explained thoroughly prior to scanning. For example, a temperature and pressure sensitive foam pillow is used to comfortably restrict head motion during scanning, thereby reducing fatigue and motion artifact. The testing and MRI session can be stopped at any time at the subject's request or due to investigator concerns about subject safety or comfort. Although there has been no demonstrated risk of MRI to fetuses, all women of childbearing age will be informed of possible unknown risks of MRI in pregnancy, and provided with an early response urine pregnancy test to use prior to scanning in order to make an informed decision as to whether to continue their participation.

Questionnaire data collection Although it is hoped that subjects will answer all questions asked, participants may choose not to answer any question and they may terminate participation at any time without penalty, which will reduce any potential emotional distress caused by having to answer a particular question.

Privacy and confidentiality In order to protect subjects' privacy regarding their participation in our studies, participants will not be scheduled in overlapping time slots. No one outside of the research team will have access to participants' data. Participants' data will only be associated with their ID numbers, not personal identifiers. Any paperwork that includes participants' names or other personal information will be stored in a locked file cabinet in the locked lab separate from the data. For each study, the electronic file linking participants' names and subject numbers will be removed from the computer and a hard copy will be archived in the sponsor's locked office when each study is completed.

Potential Benefits of the Proposed Research to Human Subjects and Others.

Potential benefits Subjects will not experience any direct benefit from participating in these studies. We anticipate that the results of these studies will improve our understanding of immediate reward bias, which is a behavioral phenotype associated with addictive disorders. Eventually this knowledge could lead to improved treatment options for people with these disorders. Participants may benefit psychologically from knowing that they are participating in medically motivated research.

Risks in relation to benefit While we have taken systematic and comprehensive precautions to reduce the risks involved in these studies, the possibility of an adverse event remains. However, any such adverse events are not expected to exceed what an average individual would experience in the course of daily life. Therefore, the potential benefits anticipated in improved treatment and management of patients with alcohol and other substance use disorders are expected to far outweigh the minimal risks associated with these studies.

Importance of the Knowledge to be Gained.

To date, the cognitive processes and neural mechanisms underlying immediate reward bias are poorly understood, but they likely play a key role in the maintenance of addiction. These studies will provide novel data on the neurobiological mechanisms regulating immediate reward bias, thus bridging this gap in our knowledge. Ultimately, such knowledge may help to identify new therapeutic approaches to treating addictive disorders. Due to the widespread occurrence of addictive disorders, their negative impact on society and the very limited number of treatments currently available, more effectively treating these diseases will substantially benefit society as a whole.

INCLUSION OF WOMEN AND MINORITIES

As noted in the Protection of Human Subjects section (*Informed Consent and Recruiting*), participants will be recruited through IRB approved flyers and advertisements distributed in the local community. Every attempt will be made to recruit women and minorities, including posting advertisements at the Sonja Haynes Stone Center for Black Culture and History; the Lesbian Gay Bisexual, Transgender Office; the Student Union; the Carolina Women's Center; and the Medical Campus buildings.

We anticipate that most subjects will come from Chapel Hill and the adjacent city of Durham. Based on the demographics of these cities (according to the U.S. Census Bureau), we estimate that participants will be: 51-55% female, 11-42% African-American, 3-12.5% Hispanic, 4.5-7% Asian American, and less than 1% (each) Native American and Pacific Islander.

For the proposed studies we will recruit participants without regard to ethnicity. Equal numbers of male and female participants will be recruited for all studies.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Now versus Later decision-making: effects of frontal development and alcohol use

Total Planned Enrollment: *60* (*40* participants for Aim *1*; *20* additional participants for Aim *2*)

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	*3*	*3*	*6*
Not Hispanic or Latino	*27*	*27*	*54*
Ethnic Category: Total of All Subjects *	*30*	*30*	*60*
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	*7*	*7*	*14*
White	*21*	*21*	*42*
Racial Categories: Total of All Subjects *	*30*	*30*	*60*

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

Both women and men of all ethnicities are eligible to participate in these studies. Based on the minority composition of the areas surrounding the University of North Carolina at Chapel Hill (averaged U.S. Census Bureau 2008 population estimate information for Durham County and Orange County, http://quickfacts.census.gov/qfd/index.html), we estimate that ~25% of the participants will be African American, ~9% will be Hispanic, ~5% will be Asian, and less than 1% combined will be American Indian or Pacific Islander (see the Targeted/Planned Enrollment Table for specific numbers of women and minorities included).

INCLUSION OF CHILDREN

These studies will recruit volunteers between the ages of 18-40, which includes children. Our recruitment area will include a college campus (UNC Chapel Hill), and the mean age for the Chapel Hill-Durham area is 24-30 years of age. Thus, our recruiting materials are expected to reach sufficient numbers of people in the 18-23 age range.

The cognitive processes that we propose to study engage the frontal lobes, an area of the brain that is not fully mature in younger children and adolescents. Thus, we do not intend to recruit children younger than 18 years of age.

Respective Contributions

I have developed this proposed study, including the theory, hypotheses and proposed methods and analysis, in collaboration with my sponsor, Dr. Charlotte Boettiger. I have written this study proposal and have consulted Dr. Boettiger for recommendations and revisions.

18. Selection of Sponsor and Institution

My undergraduate research experience in the basic behavioral neuroscience lab of Dr. Judith Grisel at Furman University sparked my interest in pursuing graduate study of the neurobiology of reward and substance misuse. My particular interest in alcohol addiction led me to the University of North Carolina at Chapel Hill (UNC), whose Bowles Center for Alcohol Studies (CAS) is one of fourteen National Research Centers funded by NIAAA. I entered graduate school at UNC via the Biological and Biomedical Science Program (BBSP), which allows students to enroll in a wide range of courses and to rotate in 3-4 labs during the first year before choosing a thesis lab and PhD program. The BBSP first-year curriculum includes a course focused on scientific ethics and presentation skills. During this course, I presented a scientific poster on one of my rotations, wrote up my findings from another rotation in journal article format, and gave a talk on my final rotation to the broader biomedical research community at UNC. I felt the experiences offered to me at UNC and in the BBSP program allowed me to find a thesis lab that best fit my research interests and gave me a strong basis in the communication skills needed to become a productive and active member in the scientific community.

The Neurobiology Curriculum at UNC focuses on broad training in all aspects of neurobiology from cellular and molecular neurobiology to cognitive psychology, consists of 70 diverse research faculty, and has demonstrated an excellence in research training as evident by the presence of a NIH training grant. Additionally, as part of the Curriculum, Neuroscience Center and CAS seminars bring in prominent scientists in these fields to discuss their work and demonstrate to students the analytical and creative skills necessary to become successful independent researchers. Due to my interest in the neurobiology of addiction and the strength of the Neurobiology Curriculum at UNC, I focused on rotating in labs affiliated with the Curriculum and CAS during my first year. Although I enjoyed my first few rotations in labs focused on using rodents to investigate the neurobiology of reward and alcohol's depressant effects, I wanted to focus on a different research paradigm for my next rotation. So, I chose to rotate in Dr. Charlotte Boettiger's lab in the Department of Psychology, which investigates the neurobiology of addiction through research with human subjects. This choice was driven by my undergraduate interest in psychology and desire to see how the neurobiology of addiction can be studied from a psychological prospective. In the Boettiger lab, I investigated a cognitive process associated with addiction: discounting of delayed rewards. I also saw the unique benefits of working with human subjects and the value of behavioral and neuroimaging techniques in investigating the underlying biological processes involved in human addiction. I joined the Boettiger lab and Curriculum in Neurobiology in May 2009 and since that time I have been eagerly engaged in further investigation of impulsive decision making (characterized by choosing smaller, immediate rewards over larger, delayed rewards in a delay-discounting task), a cognitive process recognized as a promising intermediate phenotype of addiction. My work focuses primarily on the tendency to select immediate over delayed rewards (i.e. immediate reward bias), including investigation of the neurobiological bases behind this bias. I feel that working in the Boettiger lab has allowed me to combine my interests in biology, psychology, and neuroscience to address a real-world problem that affects millions of Americans – alcohol addiction.

Dr. Boettiger is an excellent advisor and mentor. She allows me to work independently but is always accessible and helpful. I like that Dr. Boettiger is a young faculty member not far removed from graduate school and her postdoctoral training. I feel that she can relate to the problems and difficulties associated with being a graduate student and can provide insight and encouragement when I encounter difficulties. I think that Dr. Boettiger also has a firm grasp of the skills necessary to be a successful independent researcher. Therefore, she has encouraged me to begin establishing myself in the scientific community by writing grants and submitting abstracts to scientific meetings. In addition to Dr. Boettiger's assistance, the two post doctoral fellows in the lab have been helpful in guiding me in my experimental planning, data analysis, and data interpretation. Additionally, the prior success of the lab's postdoctoral fellows in applying for and obtaining NRSA support – *one receiving a postdoctoral fellowship in August 2010 from NIDA and the other receiving a strong priority score on her August 2010 submission to NIAAA* – has encouraged me to seek out funding of my own and suggests to me that the lab's research is deserving of NIH support.

The collaborative nature of the Boettiger lab has provided me an excellent place to grow as a young scientist. I feel that the resources within my Sponsor's lab and elsewhere at UNC will prepare me for a successful career as an independent researcher. The expertise of the Bowles Center for Alcohol Studies and Biomedical Research Imaging Center in particular will allow me to apply neuroimaging techniques to understanding the neurobiological mechanisms of impulsive decision making and the relationship of alcohol use to this behavior.

19. Responsible Conduct of Research

During my first year in graduate school as part of the BBSP program at UNC, I took a seminar course that included didactic training in research ethics. During the year-long course we focused on diverse ethical topics, including: authorship, proper use of animals and humans in research projects, the importance of the institutional review board, and scientific honesty. This course was designed to satisfy the NIH requirement for training in the responsible conduct of research. In addition to this introductory seminar on scientific ethics, I have completed training necessary to work with human subjects at UNC including being briefed and familiarized with HIPPA and the importance of confidentiality and safe data storage techniques as part of the Collaborative Institutional Training Initiative (CITI) Program of research ethics training. *In addition to these previous experiences in the responsible conduct of research, I am currently taking a research ethics course through the Graduate School at UNC (Grad 721) that focuses on concepts, rules, and issues that are central to research ethics. Through discussion of case studies with fellow graduate students, the course seeks to allow for a forum for discussing how to deal with ethical issues in an academic setting and has been constructed to satisfy the NIH requirement for training in the responsible conduct of research.* Additionally, I plan to take statistics courses in the future which will emphasize the importance of proper data analysis and interpretation techniques. Through seminars and continuing education received through the Curriculum in Neurobiology and Bowles Center for Alcohol Studies, I will be exposed to proper research practices and have access to faculty and other researchers with which to discuss ethical issues that arise in research. My sponsor also regularly attends these seminars and is available for me to discuss ethical questions regarding research at any time. Thus, I have received and will continue to receive excellent training on ethical integrity in research as a student at UNC.

7. Goals for Fellowship Training and Career

My career goal is to become the principal investigator of my own lab at a research university. I plan to couple my knowledge of the basic behavioral neuroscience and neurobiology of alcohol use in animal models with the expertise I will obtain in human research and neuroimaging techniques in the course of my thesis work. I envision running a lab that uses a variety of experimental approaches to investigate the neurobiology of alcohol use at a level that is directly applicable to human disease treatment. This proposed research plan will enable me to gain experience in *functional magnetic resonance imaging (fMRI)* and provide me with valuable knowledge in this area of neuroimaging. In addition, the proposed research will allow me to work with human subjects extensively and deal with the many unique challenges that accompany this type of research.

While pursuing my thesis research in the Boettiger lab, I plan to continue to supervise undergraduate research assistants and to develop my teaching skills. *I received a graduate mentor award from the UNC Office of Undergraduate Research to supervise an undergraduate student during a 2010 summer research fellowship in which she assisted me in my research. She is continuing to assist me in the current academic year as part of her honors thesis.* In addition to mentoring undergraduate students, I plan to gain experience in teaching while at UNC. *I will serve as an instructional assistant for a general psychology class during the Spring 2011 semester and may pursue additional instructional opportunities through the Psychology department in the coming years.* Additionally, to further my career goals, I will make use of the Center for Faculty Excellence (CFE) at UNC, which offers workshops focused on developing skills that will make graduate students more effective future teachers. The Future Faculty Fellowship Program offered through the CFE prepares graduate students for their first experience as independent instructors and helps them understand the roles and responsibilities they will have as faculty members in higher education. This program is an example of the skills I hope to obtain through the offerings of the CFE at UNC.

As a student in the Curriculum in Neurobiology, I will have many opportunities to present my research and improve my scientific communication skills. The Curriculum sponsors a Tuesday Miniseries that features student presentations in addition to an annual research day where students in the Curriculum present posters focused on their current research. Also, the Behavioral Neuroscience program in the Department of Psychology holds weekly seminars and invites students to present their findings. *I presented some of my current research to this group in April 2010* and will continue to share my research in this forum in years to come. Presenting to such diverse groups as cellular and molecular neurobiologists and clinical psychologists will help me to frame my research and findings in ways that are understandable to a broad range of scientists. Such experience in presenting and explaining my research in a broad and general manner will prove useful in preparing journal articles and grants, essential skills for an independent investigator.

In addition to these offerings at UNC, I plan to attend annual meetings of the Research Society on Alcoholism (RSA), Society for Neuroscience (SFN), and Cognitive Neuroscience Society (CNS) to present my research and network with other scientists engaged in similar research areas who can offer insight and advice regarding my research projects. I was fortunate to have training grant support from NIDA through the Behavioral Neuroscience program to fund my travel to the 2010 CNS and RSA meetings to present posters on my current work. I hope that presenting my work at these meetings will allow me to meet faculty members at other institutions with whom I wish to pursue postdoctoral training or to join later as a faculty colleague. Additionally, such faculty members may be interested in forming research collaborations that could be useful in strengthening my current thesis project, perhaps by using animal models to investigate the neurobiology of immediate reward bias in a more invasive manner than is possible in human research.

I think the emphasis on scientific presentations in the Curriculum in Neurobiology, offerings for teaching experience at UNC, and commitment of my sponsor and the university to send me to annual research meetings to present my research and network with other scientists will allow me to reach my goal of becoming an independent principal investigator at a leading research university. In addition, the experience I will receive in neuroimaging data collection and analysis to complete the proposed research will allow me use this powerful technique to understand the neurobiology of decision-making in humans *at risk for developing* alcohol use disorders. I will also be able to bring these newly-acquired skills with me as I undertake a postdoctoral fellowship and later set up my own research laboratory as a principal investigator.

9. Activities Planned Under This Award

Year	Research	Course Work	Teaching	Clinical
First	80%	*10%*	*10%*	
Second	90%		*10%*	
Third	*100%*			

Briefly explain activities other than research and relate them to the proposed research training.

While I will have completed all of my course requirements for the Curriculum in Neurobiology, during the period of this fellowship, I plan to take a short course or workshop in neuroimaging techniques to gain expertise in MRI data collection and analysis. In addition, I plan to take graduate level biostatistics courses offered through the UNC School of Public Health to increase my knowledge of proper data analysis approaches. *To assist me in my study of young adult brain development and the cognitive processes of addiction, I intend to take a few courses offered through the Department of Psychology and Neuroscience at nearby Duke University: Developing Mind and Brian (PSY 147S) and Functional Anatomy of the Human Brian (PSY 146S). These courses will increase my knowledge of developmental cognitive neuroscience (PSY 147S) and brain anatomy (PSY 146S) and augment my research training in fMRI, decision making, and late adolescent cognitive and brain development.* In addition, both the Behavioral Neuroscience Program and the Bowles Center for Alcohol Studies at UNC have well-established training programs in place that focus on addiction, and I will take part in course and seminar offerings from both to broaden my knowledge in the area of addiction. *Such courses may include Neuropharmacology of Alcohol and Substance Abuse (PHCO 728), taught by Dr. Leslie Morrow of the Alcohol Center, for example. In addition to serving as an instructional assistant for a general Psychology course in Spring 2011,* I plan to serve as a teaching assistant in either the Department of Biology or Psychology at UNC to gain some additional teaching experience before receiving my PhD. All of these experiences should aid me in obtaining the proper training to achieve my goal of becoming an academic research scientist.

10. Doctoral Dissertation and Other Research Experience

My research experience began in a basic behavioral neuroscience lab at Furman University during the summer before my senior year of college. I chose to work in the lab of Judith Grisel, where I assisted in the experimental planning, data collection, and data analysis of three interrelated experiments. First, I used *in vivo* microdialysis and HPLC to detect strain differences in baseline dopamine and glutamate levels in the nucleus accumbens of three different strains of mice transgenic for β-endorphin. I also investigated how levels of these transmitters are altered by acute alcohol (EtOH) administration. Second, I used behavioral tests to analyze behavioral despair (a mouse model of depression) and anxiety in these same strains to determine the role of β-endorphin and EtOH in influencing these mice's behavior. Third, I used conditioned place preference experiments to compare the reward value of EtOH in these mouse strains and thus whether β-endorphin affected the mice's propensity to associate EtOH with reward. While in the lab I became proficient in animal husbandry, experimental design, data analysis, and scientific communication techniques. I received funding for this summer research project from the South Carolina NIH-IDeA Networks of Biomedical Research Excellence (INBRE), which provided the opportunity to present my research to a group of fellow students and faculty members. In addition to this experience, I gave a talk in July 2007 entitled "Evaluating the neurocircuitry of β-endorphin mediated reinforcement in the nucleus accumbens using transgenic mice" to a group of faculty and peers at the First Annual Summer Research Conference Between Furman and Davidson Universities. When I completed my research in September 2007, I prepared a poster ("Role of β-endorphin in behavioral despair, stress, and anxiety") to present at the 2007 Annual Meeting of the Society for Neuroscience Faculty for Undergraduate Neuroscience Poster Session. During the 2007-8 academic year, I also presented my findings from this summer research at other conferences including the South Carolina NIH-INBRE 2008 Research Symposium in January 2008 and the Symposium for Young Neuroscientists and Professors of the SouthEast (SYNAPSE) meeting in March 2008. My work in the Grisel lab also received an acknowledgement in a recent paper from the lab: Grisel JE, et al. (2008). Influence of *β*- endorphin on anxious behavior in mice: interaction with EtOH. *Psychopharmacology*, *200*, 105-115. This initial research experience at Furman, which included presenting my findings to the broader scientific community, laid the foundation for my interest in continuing conducting scientific research related to understanding the neurobiology of alcohol addiction and making this the focus of my future academic and career interests. To continue focusing on understanding the neurobiology of alcohol addiction, I chose to pursue graduate studies at the University of North Carolina at Chapel Hill.

My research at the University of North Carolina at Chapel Hill began with rotations in four labs affiliated with the Curriculum in Neurobiology beginning in June 2008 and ending in May 2009. During my first rotation, in Mark Wightman's lab in the Chemistry Department, I used fast-scan cyclic voltammetry to investigate changes in dopamine in the nucleus accubmens of rats in response to natural rewards. My experiences in the Wightman lab included performing surgeries to insert the guide for the recording electrode, stimulating electrode, and reference electrode used in the voltammetry procedure, learning the program used to stimulate and record the electrical signature of dopamine in the rat brain, and conditioning rats to press for sugar pellets in the operant conditioning chambers used in the later parts of the study. This experience taught me a great deal about measuring dopamine levels with high temporal resolution.

My second rotation was in the lab of Clyde Hodge in the Psychiatry and Pharmacology Departments. Here, I studied the relationship between depression and EtOH in mice through behavioral and immunohistochemical techniques in an effort to understand the cell signaling pathways altered in response to acute i.p. injections of EtOH. While in the Hodge lab, I used an automated Forced Swim Test apparatus from BIObserve to measure depressant-like behaviors in control mice given i.p. EtOH injections and performed immunohistochemistry on brain tissue from these mice to look for increases in active protein kinases and their downstream targets following EtOH administration. My work in the Hodge lab complimented and extended the behavioral neuroscience work I had done in the Grisel lab at Furman and provided me an example of how behavioral neuroscience research can be coupled with cell signaling techniques to investigate the cellular mechanisms associated with behavior and EtOH's effect on these mechanisms and behavior.

During my third rotation in Charlotte Boettiger's lab in the Psychology Department, I studied the effect of dopamine on prefrontal cortex function in a decision-making task by taking advantage of state-related changes in dopamine via estrogen fluctuations in the female menstrual cycle. I also investigated how variations in the catechol-O-methyltransferase (COMT) gene affected performance on a decision making task employed in the lab. While rotating in the Boettiger lab, I learned firsthand about issues important in human research such as Institutional Review Board approval and subject confidentiality. I also became familiar with the programs utilized in the lab to create our experiments (E-Prime) and compile and summarize our data (MatLab). Working

in the Boettiger lab showed me the potential of human behavioral neuroscience research and how neuroimaging techniques coupled with behavioral tasks can be used to investigate the neurobiology underlying behaviors (such as immediate reward bias) known to be abnormal in alcohol abusers. Since my academic background at Furman was heavily focused on psychology and biology, I found the type of research taking place in the Boettiger lab to successfully combine these two areas that I had enjoyed learning about as an undergraduate. Thus, her lab felt like the perfect fit for me and the place where I would want to conduct my thesis research.

My fourth and final rotation occurred in Patricia Maness's lab in the Biochemistry Department. While in the Maness lab, I investigated the role of the L1 cell adhesion molecule and Eph/ephrin signaling in early axonal targeting. I performed growth cone collapse assays using EphrinA-EphA growth cone retraction signaling to see if cortical neurons from L1 null mice collapsed similarly to the cortical neurons of wild-type mice. Additionally, I sought to identify the binding site on L1 for the EphA4 receptor using coimmunoprecipitation experiments. This experience was useful in that it exposed me to cellular and molecular biology techniques with which I was unfamiliar and gave me the knowledge to better understand this type of research when I encounter it in the scientific literature.

Since joining the Boettiger lab in May 2009, I have been continuing to investigate the neurobiological basis of immediate reward bias and have had two first-author abstracts accepted to national meetings (Cognitive Neuroscience Society and Research Society on Alcoholism) focused on work I have done during my first full year in the lab. *I am currently preparing several manuscripts for publication based on my preliminary studies in the lab. I am the first author on two of these manuscripts, which are derived from the studies that produced much of the preliminary data for this application, and a contributing author for two additional manuscripts. In addition, the project that I began during my rotation is nearly complete, and I expect to prepare a first author manuscript based on that study in early 2011.* In addition to continuing to investigate the role of dopamine on prefrontal cortex function and performance on our delayed-discounting decision making task, I have begun investigating the effect of age and frontal cortical development on our decision making task – the subject of this NRSA research proposal. I have found significant differences in the decision-making behavior of late adolescents/young adults *(ages 18-23)* relative to older adults' *(25-40). Moreover, we also find that adults who drink heavily, but do not meet DSM-IV criteria for alcohol dependence make decisions more like those of late adolescents*. I *now plan* to *identify the functional brain differences associated with these behavioral differences*. *I have recently begun acquiring fMRI, sMRI, and DTI data in our imaging facility while subjects perform the delay-discounting task that I will use in my proposed research. I am thus familiar with the imaging protocols, data collection, and data storage techniques that my proposed studies will require. Furthermore, with guidance from Dr. Boettiger and the postdoctoral fellows in the lab, I have begun using SPM 8 to pre-process the structural and fMRI data that I have collected and am learning the proper approach for analyses of these data. These experiences will provide me with the tools needed to collect and analyze the fMRI data for the proposed studies.*

I feel the line of research I am working on in the Boettiger lab combines my initial undergraduate interest in psychology, biology, and behavioral neuroscience research while allowing me to learn powerful neuroimaging techniques that will be invaluable to me as I move forward in my academic career. I see myself eventually having my own research lab dedicated to using neuroimaging techniques to study the neurobiology of addiction in humans while possibly conducting complementary, invasive studies in rodents to further delineate the neurobiology of addiction. I hope that my work can eventually lead to a better understanding of the neurobiology of alcohol addiction *and how immaturity of the brain in early adulthood may contribute to greater immediate reward bias and whether heavy drinking is associated with delayed brain maturation. As the tendency to favor immediate rewards may promote alcohol misuse, such brain differences may help to explain why young adults and heavy drinkers are at increased risk for developing alcohol use disorders. Such an understanding of the role of brain development and heavy alcohol use on a cognitive process believed to relate to compulsive drug use and alcohol use disorders could allow for more targeted interventions for young adults at greatest risk for developing alcohol dependence in adulthood. Identifying such high-risk youth early in the establishment of problem drinking habits may eventually reduce the number of individuals developing alcohol use disorders in adulthood.*